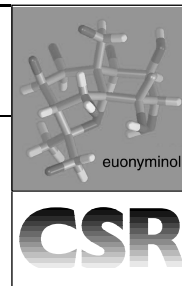


Celastraceae sesquiterpenoids: biological activity and synthesis



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Plant extracts of the Celastraceae have been used for centuries throughout South America and China as insect repellents and insecticides in traditional agriculture, and also for the treatment of a plethora of medical ailments from stomach complaints and fever to rheumatoid arthritis and cancer. Many of the medicinally interesting properties associated with these crude preparations have now been attributed to a large family of highly oxygenated sesquiterpenoids based on a tricyclic dihydroagarofuran skeleton. In this article, the structural diversity and range of biological activities associated with this intriguing class of natural products are examined with a view to stimulating interest in their total synthesis. Existing synthetic endeavours towards their synthesis are also evaluated.

1 Background and introduction to the Celastraceae

The Celastraceae family is indigenous to tropical and subtropical regions of the world, including North Africa, South America, and many parts of East Asia, particularly China.^{1,2} The family constitutes approximately 88 genera and 1300 species of plants.³ These plants generally grow as small trees, bushes, or lianas and have resinous stems and leaves. They have

been valued since antiquity because their extracts have useful medicinal properties.⁴ Indeed, the variety of properties attributed to crude plant extracts of the Celastraceae in traditional medicine and agriculture is astonishing, and includes stimulant, appetite suppressive, sedative, emetic, purgative, memory-restorative, male contraceptive, anti-tumour, anti-leukemic, anti-bacterial, insecticidal and insect repellent activities!⁵ For example, extracts of the bark of the thunder-god vine *Tripterygium wilfordii* have been used by the Chinese for centuries to combat life-threatening illness, and have more recently found application in the treatment of leukemia and rheumatoid arthritis.⁶ Similarly, the stimulating properties of the leaves of the khat bush *Catha edulis*, which grows in certain parts of East Africa and Southern Arabia, were reported in the literature as early as 1237 by the physician Naguib Ad Din, who proposed the use of khat for alleviating depression.⁷ Since khat leaves rapidly lose their effect after picking, the culture of chewing khat leaves for their stimulant/euphoric and appetite/fatigue suppressive effects was for centuries confined to the immediate areas where the plant grows.⁷ With improvements in road communications, however, the habit had become so widespread by the mid-1970s that a form of addiction known as khatism was beginning to present serious social and economic difficulties in Ethiopia and the Yemen Republic.⁴ This prompted the World Health Organisation to fund an investigation to determine the active constituents of khat. It was this program,⁸ and the coincidental discovery in 1972 of the macrolide maytansine from

Alan Spivey (left) received a BSc in chemistry in 1988 from the University of Nottingham and a DPhil in 1991 from the University of Oxford under the guidance of Professor Sir Jack Baldwin. After post-doctoral work at the Université de Genève, Switzerland with the late Professor Wolfgang Oppolzer, and at the University of Cambridge with Professor Sir Alan Battersby, he moved to a lectureship at the University of Sheffield where he is currently a reader. Research in his group is focused on the development of new catalysts for asymmetric acylation, new linkers for solid phase organic synthesis, chemical aspects of

signal transduction, and total synthesis, e.g. of biologically active Celastraceae sesquiterpenoids.

Matthew Weston (centre) received an MChem in chemistry in 1998 from the University of Sheffield and is currently in the third year of research towards a PhD exploring approaches to the total synthesis of bioactive Celastraceae sesquiterpenoid cores under the direction of Alan Spivey.

Steven Woodhead (right) received a BSc in chemistry in 1995 and his PhD in 1999, under the direction of Alan Spivey, at the University of Sheffield where he initiated the Celastraceae total synthesis program. After post-doctoral research at Florida State University with Professor Robert Holton, he returned to the UK for a further period of post-doctoral study with Professor Gerald Pattenden at the University of Nottingham. He is currently working in medicinal chemistry research with Astex-technology in Cambridge, UK.



Maytenus ovatus, which displayed exceptionally high inhibitory activity *in vitro* against certain human carcinomas,⁹ that catapulted the natural product chemistry of the Celastraceae into the limelight.

Over the last 30 years or so, a large number of secondary metabolites exhibiting a wide range of bioactivity have been extracted from the Celastraceae. In addition to numerous terpenoids, including a diverse array of sesquiterpenoids which constitute the focus of this article, various bioactive phenyl-alkylamines, maytansinoids, and flavonoids have also been isolated^{5,10} (Fig. 1).

In particular, the α -aminoketone (–)-cathinone has now been established to be the unstable constituent of fresh khat leaves which is primarily responsible for their stimulant and euphoric effects.¹⁰ (–)-Cathinone is structurally related to, and has the same absolute configuration as, (+)-amphetamine and (+)-norpseudoephedrine but is a more potent stimulant.⁷ The development of maytansine† and related macrolides as anti-tumour leads was halted in the 1980s when they were found to cause serious gastro-intestinal damage in rats,⁵ but recent advances in drug targeting *via* conjugation to cancer-specific humanised antibodies appear to offer new opportunities for clinical application.¹¹ The flavonoid quercetin, which is also found in a number of other plant families, displays a wide spectrum of anti-oxidant and anti-inflammatory activity as a result of its ability to quench reactive oxygen radicals.¹⁰

† It has been suggested that maytansine may not be a plant secondary metabolite of the Celastraceae and that it is in fact derived from associated fungi/bacteria.⁵

The bulk of the bioactive constituents of the Celastraceae, however, are terpenoids. Terpenoids are a structurally diverse class of secondary metabolites composed from an integral number of biological equivalents of the C₅ hydrocarbon isoprene (2-methylbuta-1,3-diene, Fig. 2). During their biosynthesis these ‘monomers’ are joined together ‘head-to-tail’ fashion, frequently with extensive subsequent modification of structure due to rearrangements and functional group changes to give characteristic and topologically related families of natural products.¹² Thus, monoterpenoids comprise two isoprene units and therefore have a C₁₀ core skeleton, sesquiterpenoids three isoprene units (C₁₅), diterpenoids four isoprene units (C₂₀), and triterpenoids six isoprene units (C₃₀). All these types of terpenoids are found in extracts of the Celastraceae (Fig. 2).

Monoterpenoids such as β -thujone are volatile compounds responsible for the characteristic odour of *e.g.* freshly picked khat leaves.¹⁰ The tri-epoxide diterpenoid triptolide was isolated from the roots of the thunder-god vine *Tripterygium wilfordii*, and has been shown to be responsible for some of the significant anti-leukemic and anti-tumour activity of this plant.¹³ Triptolide also displays interesting male anti-fertility properties and is one of a number of diterpene epoxides contained in a commercially available ‘total multi-glycoside extract’ of *Tripterygium wilfordii* that has been used clinically for male fertility control in China.^{14,15} The triterpene tingenone and related quinone methides display cytotoxic and anti-bacterial activity which is believed to be the result of DNA intercalation and nucleophilic addition by DNA bases.¹⁶

The most pervasive and characteristic metabolites of the Celastraceae, however, are a large family of unusually highly

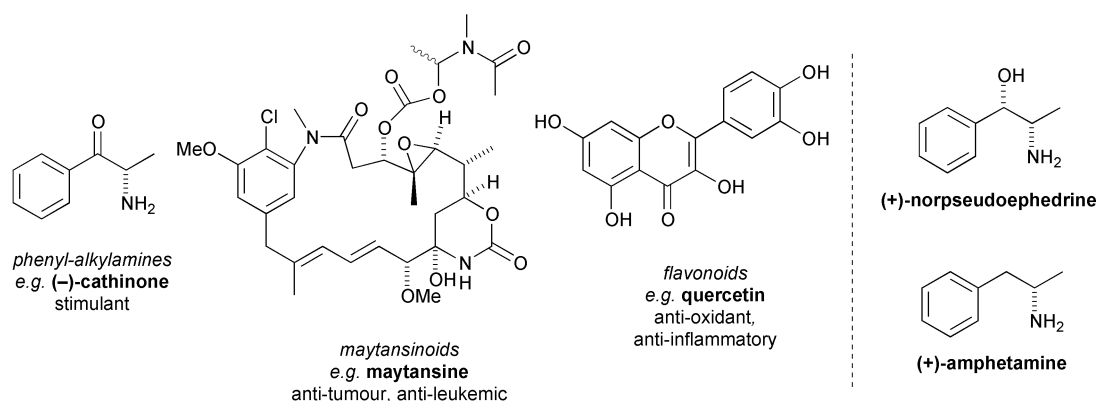


Fig. 1 Non-terpenoid secondary metabolites of the Celastraceae, and the structures of norpseudoephedrine and amphetamine.

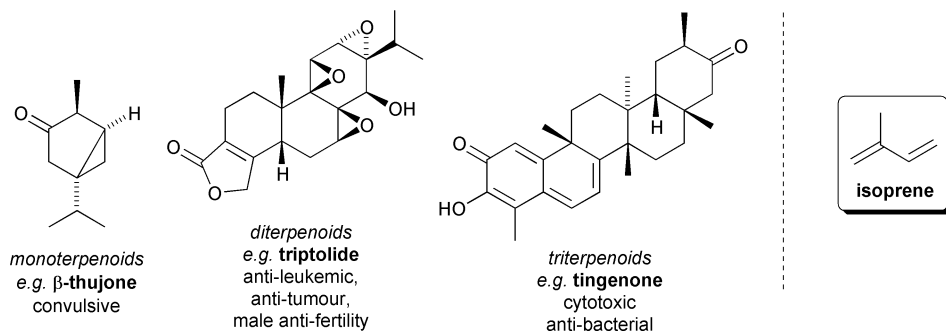


Fig. 2 Mono-, di-, and triterpenoid metabolites of the Celastraceae, and the structure of isoprene.

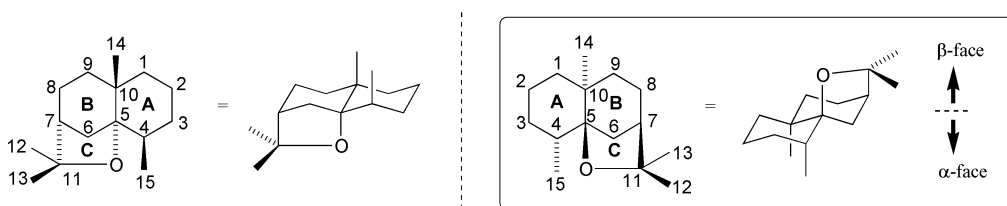


Fig. 3 The dihydroagarofuran skeleton.

oxygenated sesquiterpenoids, and it is this class of compounds that has attracted the most interest. The remainder of this article overviews the structural diversity displayed by this class of natural products, the extent of their biological activities, and details the most significant synthetic endeavours towards their total synthesis. Particular attention is focused on methods used to construct the tetrahydrofuran C-ring of the dihydroagarofuran skeleton (see next section), as this structural feature is not found in other sesquiterpenoids.

2 The diversity of Celastraceae sesquiterpenoid structures

Celastraceae sesquiterpenoids generally occur as poly-esters of variously poly-oxygenated tricyclic scaffolds all based on a core

C_{15} skeleton known as dihydroagarofuran.^{17–19}† This skeleton comprises A and B rings in the form of an axially dimethylated *trans*-decalin bicycle with a 1,3-diaxially fused, Me_2C-O bridge constituting the tetrahydrofuran C-ring. Throughout this review the dihydroagarofuran ring system is drawn such that the C-ring is on the *bottom* face of the molecule, as depicted unboxed on the left-hand side of Fig. 3. This elevation has been

† (–)-Dihydroagarofuran is itself a natural product found in galbanum resin and sandalwood oil.⁴ It is sometimes referred to as (–)-dihydro- β -agarofuran. The β designation here refers to the fact that it is the major isomer obtained by catalytic hydrogenation of (–)- β -agarofuran, which has a double bond between C-4 and C-15.^{17,18} Similarly, (–)-isodihydroagarofuran (which is epimeric at C-4) is sometimes referred to as (–)-dihydro- α -agarofuran as it is the major isomer obtained by catalytic hydrogenation of (+)- α -agarofuran, which has a double bond between C-3 and C-4.^{17,18} (+)- α -Agarofuran occurs in agar wood oil.¹⁹

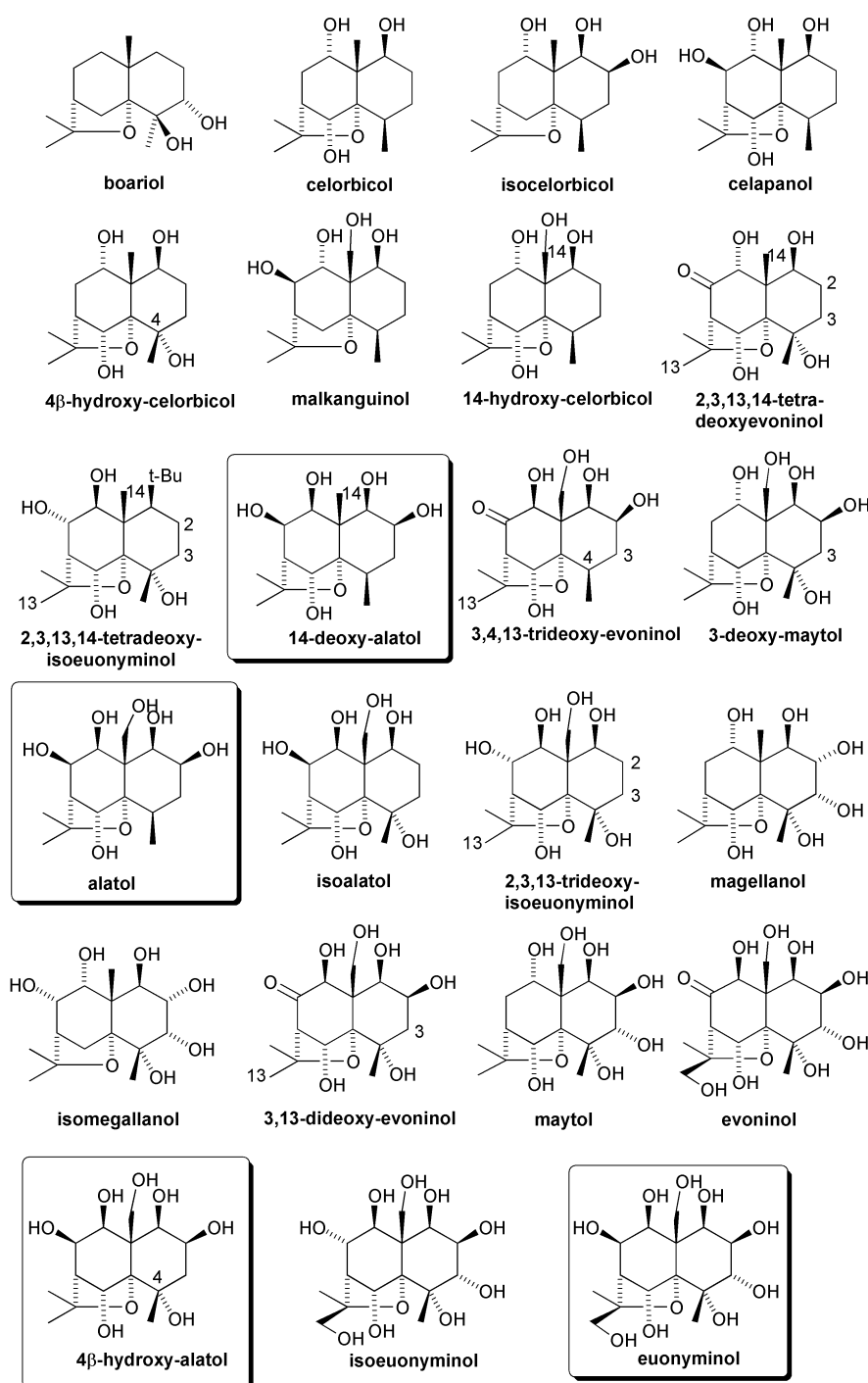


Fig. 4 Some polyhydroxy dihydroagarofuran sesquiterpenoid cores. Those with symmetric hydroxylation across the 'northern' periphery are boxed.

used because it corresponds to that most commonly employed in literature of the Celastraceae, and particularly in the seminal isolation studies of Crombie *et al.*,⁴ the defining synthetic studies of White *et al.*,²⁰ and the extensive biological screening studies of Takaishi *et al.*⁶ (*vide infra*).

It is important to note, however, that the alternative elevation in which the C-ring is on the *top* face of the molecule, as depicted in the box on the right-hand side of Fig. 3, corresponds to the conventional presentation of terpenoid and steroid structures. § A number of authors including Brüning,¹ Büchi,¹⁸ Gonzalez,²¹ and Huffman²² have adhered to this convention. Two numbering regimes have also been employed in the literature of the Celastraceae. The most prevalent by far, and that used throughout this review, is illustrated in Fig. 3. ¶ The

§ This convention, which engages when the absolute configuration at C-7 is known, places the C-7–C-11 bond in a β -linked orientation, places C-1 as the top left carbon, and labels this ring as the A-ring. The α - and β -face designation and the numbering regime employed (see Fig. 3) are tied to this convention.

¶ It should also be noted that in the numbering regime shown in Fig. 3 the designations of C-14–C-15, and of C-12–C-13 are sometimes interchanged.

alternative regime is defined in the publications of Yamada²³ and Takaishi.⁶ The enantiomer of agarofuran depicted in Fig. 3 has the correct absolute configuration for naturally occurring (–)-dihydroagarofuran,¹⁷ and all the dihydroagarofurans of the Celastraceae for which determinations have been made [*e.g.* (–)-euonyminol^{24–27}].

Well over 200 members of this chemical class have now been characterised, based on over 40, variously oxygenated dihydroagarofuran core structures. These core structures can have as few as two additional oxygen containing groups, as in the case of boariol, or as many as nine, as in the case of euonyminol (Fig. 4).^{2,4,5}

The peripheral esterifying residues vary widely from acetic (Ac) and benzoic (Bz) acids through more complex aliphatic and heterocyclic acids to stereochemically elaborate pyridine-containing dicarboxylic acids (and a monoterpene diacid)¹⁵ which invariably form macrodilactone bridges between C-3 and C-13 and/or C-8 and C-14 (Fig. 5). The relative position, number, and configuration of these residues distinguishes each individual sesquiterpenoid. ||

|| An asterisk denotes a stereogenic centre for which the absolute configuration from a Celastraceae natural product has yet to be determined.

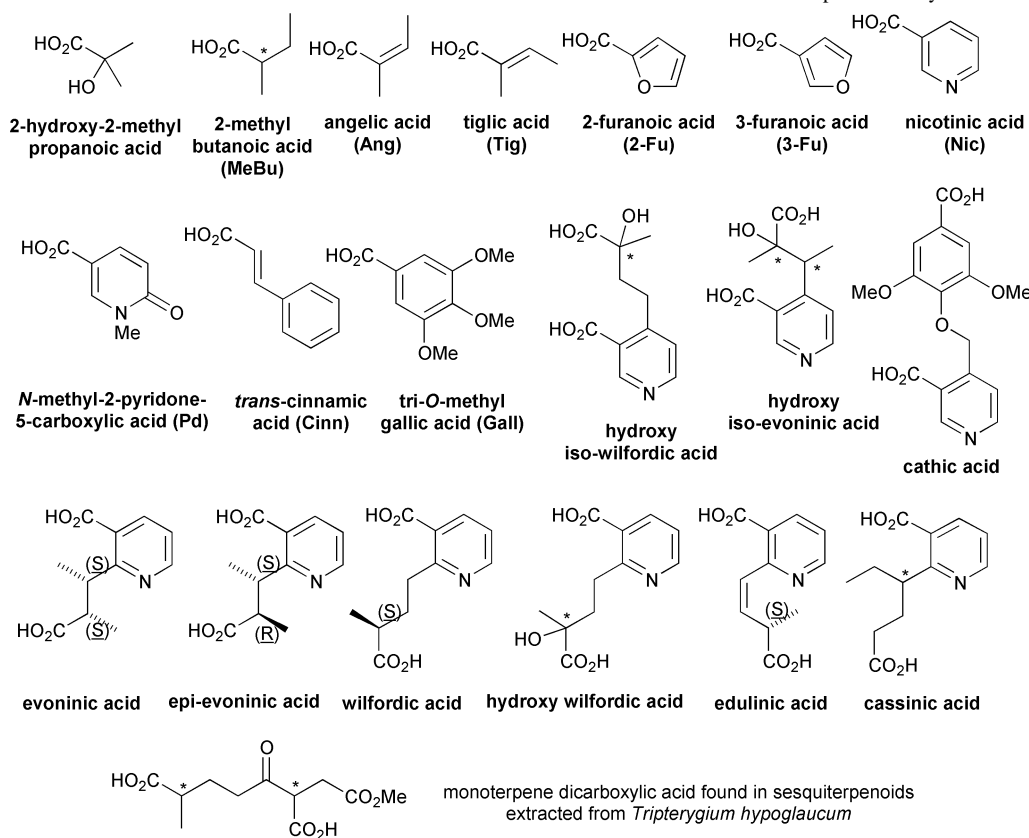


Fig. 5 Esterifying residues found in Celastraceae sesquiterpenoids.

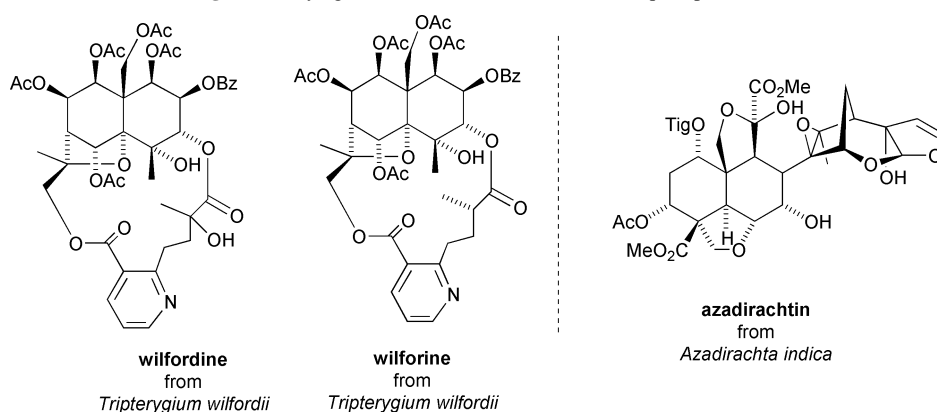


Fig. 6 Insecticidal/anti-feedant Celastraceae sesquiterpenoids from *Tripterygium wilfordii* and the structure of azadirachtin.

Four core structures: 14-deoxyalatal, alatal, 4 β -hydroxyalatal, and euonyminol have been highlighted in Fig. 4. This is because they have a symmetric array of hydroxylation across the α -face of their 'northern' periphery. As will become apparent in the following overview of biological activity, Celastraceae natural products comprising these cores invariably display interesting activity. It was this observation, combined with the notion that such latent symmetry might be exploited to facilitate their synthesis, which inspired our own synthetic program towards the total asymmetric synthesis of these Celastraceae sesquiterpenoid cores (see Scheme 13).

3 Biological activity of the Celastraceae sesquiterpenoids²⁸

3.1 Insecticidal and insect anti-feedant activity

Various species of Celastraceae have been used in traditional Chinese agriculture for centuries to protect crops against insect damage.²⁹ The first insecticidal constituents were isolated from extracts of *Tripterygium wilfordii* and characterised as the sesquiterpenoids wilfordine and wilforine.³⁰ These alkaloids, which are based on the euonyminol core, were found to be highly toxic towards the larvae of the European corn borer *Pyrausta nubilalis* at concentrations of 60 ppm (100% mortality after 3 days).³¹ Additionally, wilforine displays effective anti-feedant activity towards cabbage leaf worm *Pieris rapae* at $1 \times 10^{-5}\%$ dry weight, and migratory locusts *Locusta migratoria* at $5 \times 10^{-5}\%$ dry weight.³² This makes wilforine more potent towards these pests than azadirachtin, the most notable insect anti-feedant from plants (which is not a Celastraceae natural product, but which comes from the Indian Neem tree *Azadirachta indica*)³² (Fig. 6).

The powdered root bark of Chinese bittersweet *Celastrus angulatus* has also yielded a number of anti-feedant sesquiterpenes, most notably celangulin which is based on the 4 β -hydroxyalatal core.³³ Celangulin exhibits activity against the fall armyworm *Mythimna separata* at 5 ppm and against the cabbage leaf worm *Pieris rapae* at 222 ppm.³³ The seed oil of *Euonymus bungeanus* and the powdered seeds of *Euonymus fortunei* have also yielded two alatal-based sesquiterpenoids which display activity against *Pieris rapae* at 200 and 1000 ppm, respectively.³⁴ A series of macrolactone-containing sesquiterpenoids, known as cathedulins and which are based on the euonyminol core, have been isolated from the leaves and twigs of the khat bush *Catha edulis*.⁴ Many of the cathedulins possess significant insect anti-feedant properties. In particular, cathedulin E-5^{††} exhibits potent activity against the pink bollworm *Pectinophora gossypiella* at 1 ppm, a value comparable with that of azadirachtin³⁵ (Fig. 7).

Recently, Gonzalez carried out a large and systematic study of insecticidal and anti-feedant activity of sesquiterpenes sourced from a variety of species of Celastraceae using the leaf disk method against the Egyptian cotton leaf worm *Spodoptera*

^{††} The E in cathedulin E-5 designates of Ethiopian origin. Similarly, K and Y designate cathedulins isolated from plants sourced in Kenya and the Yemen Republic, respectively.

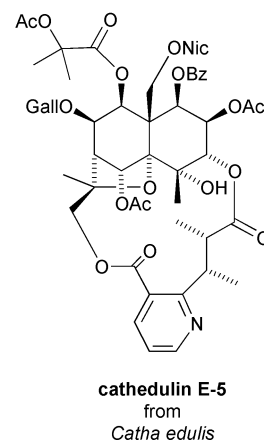
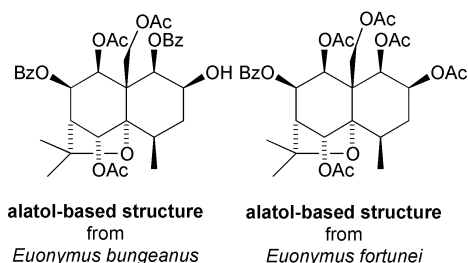
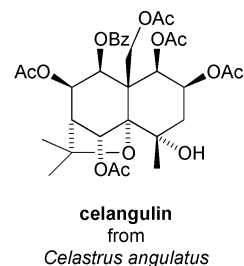


Fig. 7 Insecticidal/anti-feedant sesquiterpenoids from *Celastrus angulatus*, *Euonymus bungeanus*, *Euonymus fortunei* and *Catha edulis*.

littoralis.²⁹ Most of the agarofuran sesquiterpenes tested showed activity at $1 \mu\text{g cm}^{-2}$, but the most active ones, based on the 4 β -hydroxyalatal and isoalatal cores, and including celangulin, were found to be active at $0.1 \mu\text{g cm}^{-2}$, and in one case at $0.01 \mu\text{g cm}^{-2}$, which is more potent than the well-known anti-feedant triphenyl tin acetate²⁹ (Fig. 8).

For compounds with the same skeleton, activity was found to vary with the nature of the esterifying residues.²⁹ The greater the number of acetyl residues, the greater the activity. The opposite was observed with benzoyl residues, where increasing frequency was observed to decrease anti-feedant activity. Compounds with aromatic esters at C-1 or C-9 were found to be only weakly active, while the introduction of esterifying residues at C-2 had no observable effect upon activity. Insecticidal activity was roughly correlated with the presence of a carbonyl group at C-8, with sesquiterpenoids having this

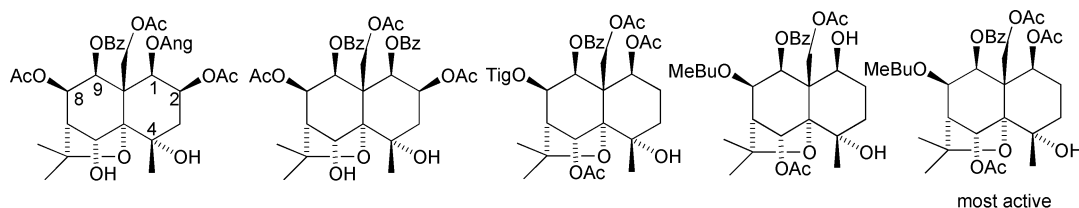


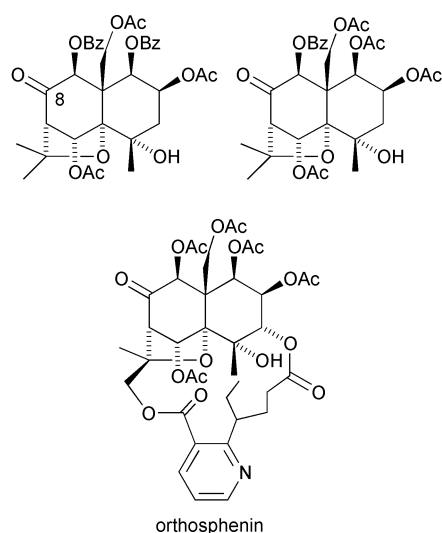
Fig. 8 Anti-feedant sesquiterpenoids from *Maytenus canariensis*.

feature isolated from *Maytenus canariensis* and *Orthosphenia mexicana* being the most potent.²⁹ The evoninol skeleton appeared to confer the greatest activity ($LD_{100} = 0.01 \mu\text{g cm}^{-2}$)^{††} (Fig. 9).

3.2 Cytotoxicity and anti-cancer activity

Plants of the genus *Tripterygium wilfordii* have been used in traditional Chinese medicine for centuries for the treatment of cancer.²¹ The presence of the anti-tumour and anti-leukemic diterpenoid triptolide¹³ (Fig. 2), and the cytotoxic triterpene tingenone¹⁶ (Fig. 2) in this genus accounts for much of this activity. However, the discovery of the anti-tumour properties of the macrolide maytansine from *Maytenus ovatus*⁹ (Fig. 1), promoted a widespread search for further Celastraceae-derived anti-cancer agents. The first to be found was celaglaumin from the bark of *Celastrus glaucophyllus* which was found to exhibit weak activity against the murine leukemia cell line L1210 (IC_{50}

^{††} The LD_{100} is the lethal dose, *i.e.* that required to kill 100% of the insects.



3,13-dideoxy-evoninol and evoninol-based structures from *Maytenus canariensis* and *Orthosphenia mexicana*

Fig. 9 Insecticidal sesquiterpenoids from *Maytenus canariensis* and *Orthosphenia mexicana*.

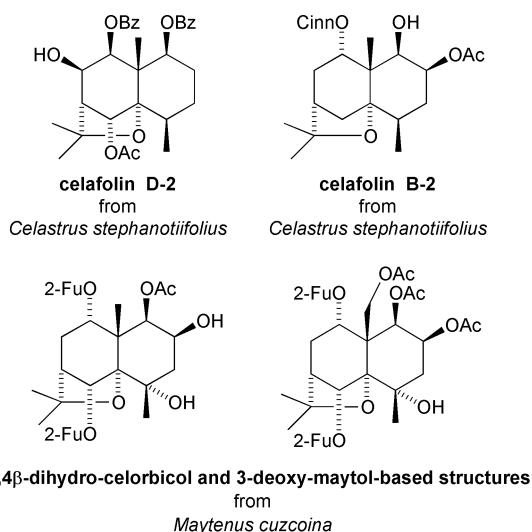


Fig. 11 Anti-tumour promoting sesquiterpenoids from *Celastrus stephanotiifolius* and *Maytenus cuzcoina*, and the structures of the anti-tumour promoters glycyrrhizin and retinoic acid.

$= 2.11 \mu\text{g mL}^{-1}$)^{§§} and the lymphatic leukemia cell line P-388 ($IC_{50} = 4.12 \mu\text{g mL}^{-1}$).³⁶ More recently, Takaishi has evaluated a number of dihydroagarofuran sesquiterpenes using an Epstein-Barr virus early antigen (EBV-EA) screen and found that triptofordin F-2 and triptogelin A-1 from *Tripterygium wilfordii* show promising anti-tumour promoting activity.³⁷ Triptogelin A-1 was shown to reduce both the incidence and frequency of skin tumours in mice without excessive cytotoxicity. From these studies it was deduced that the functionalities at C-6, C-14 and C-8 play an important part in the inhibition of EBV: an acetyl residue at C-6 confers greater activity compared to an alcohol, while a nicotinoyl residue is optimal. The presence of C-14 as an acetoxymethyl group also appears to confer superior activity compared to having a methyl group at this position³⁷ (Fig. 10).

EBV-EA activation inhibition has also been reported for celafolins D-2 and B-2 isolated from the seeds of *Celastrus stephanotiifolius*,³⁸ and for a series of 2 α ,4 β -dihydrocelorbicol and 3-deoxymaytol-based sesquiterpenoids from the fruits of *Maytenus cuzcoina*²¹ (Fig. 11).

The *Maytenus cuzcoina*-derived compounds show more significant inhibition in Raji cells than standard anti-tumour

^{§§} The IC_{50} is the inhibitory concentration required to kill 50% of cells *in vitro*.

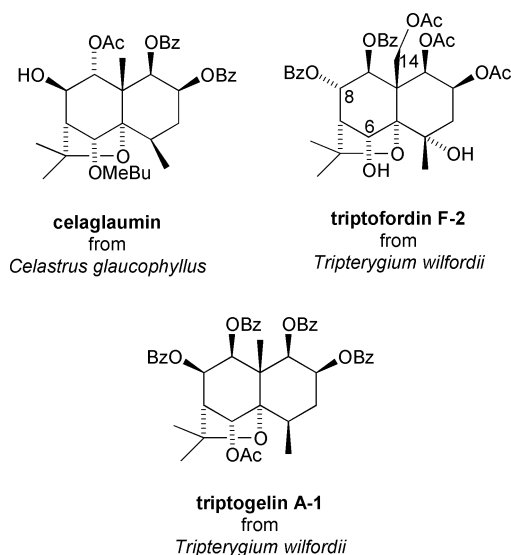
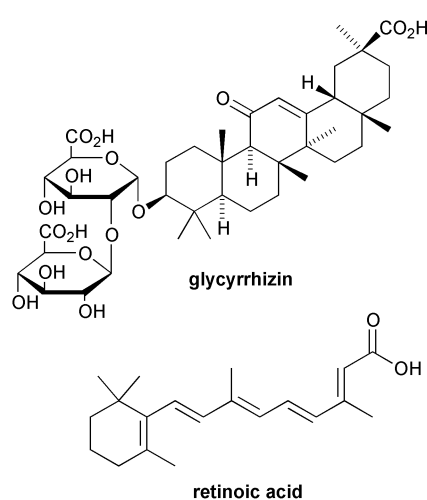


Fig. 10 Anti-tumour promoting sesquiterpenoids from *Celastrus glaucophyllus* and *Tripterygium wilfordii*.



promoters such as glycyrrhizin and retinoic acid.²¹ The 3-deoxymaytol-based derivative was found to be the most active and moreover, inhibitory activity within the dihydrocelorbicol series was strongly influenced by the nature of esterification at the C-2 position: OAc > O(2-Fu) > OH > OMeBu.²¹

A series of dilactone bridged dihydroagarofuran structures, including emarginatine-A and emarginatine, which were isolated from the stems and branches of *Maytenus emarginata*, have also been shown to display *in vitro* cytotoxicity against the human epidermoid carcinoma of the nasopharynx KB (ED₅₀ = 0.4–4.0 μg mL⁻¹).³⁹ Emarginatine-A, which is based on the euonyminol skeleton and contains a C-3–C-13 evononic acid dilactone bridge, was slightly less active than emarginatine, which differs only by containing a C-3–C-13 hydroxywilfordic acid dilactone bridge (ED₅₀ = 4.0 vs. 2.1 μg mL⁻¹, respectively).³⁹ Emarginatine-F, which is based on the iso-euonyminol skeleton, showed more potent activity against the human epidermoid carcinoma of the nasopharynx KB (ED₅₀ = 0.51 μg mL⁻¹), and also showed significant activity against the human colon adenocarcinoma cell line HCT-8 (ED₅₀ = 1.29 μg mL⁻¹), the human medulloblastoma cell line TE-671 (ED₅₀ = 0.21 μg mL⁻¹), and the murine lymphocytic leukemia cell line P-388 (ED₅₀ = 0.69 μg mL⁻¹).⁴⁰ A related macrolide, celahinine A, was also found to be present in a crude ethanolic extract of *Celastrus hindsii* which displayed potent *in vitro* cytotoxicity against human nasopharynx-, cervix-, and colon-carcinoma cell lines⁴¹ (Fig. 12).

3.3 Reversal of multi-drug resistance (MDR)

Celastraceae sesquiterpenoids have also been found to display interesting reversal of multi-drug resistance (MDR) in cancer cells. MDR is a major problem in chemotherapy treatments for various cancers.⁴² A number of compounds, including celafolin A-1 and celorbicol, have been isolated from *Celastrus orbiculatus* which reverse, either partially or totally, resistance to adriamycin, vinblastine, and paclitaxel in the human nasopharynx carcinoma cells KB-V1 and the human breast cancer cells

¶¶ The ED₅₀ is the effective dose required to effect a 50% reduction in viable cells *in vivo*.

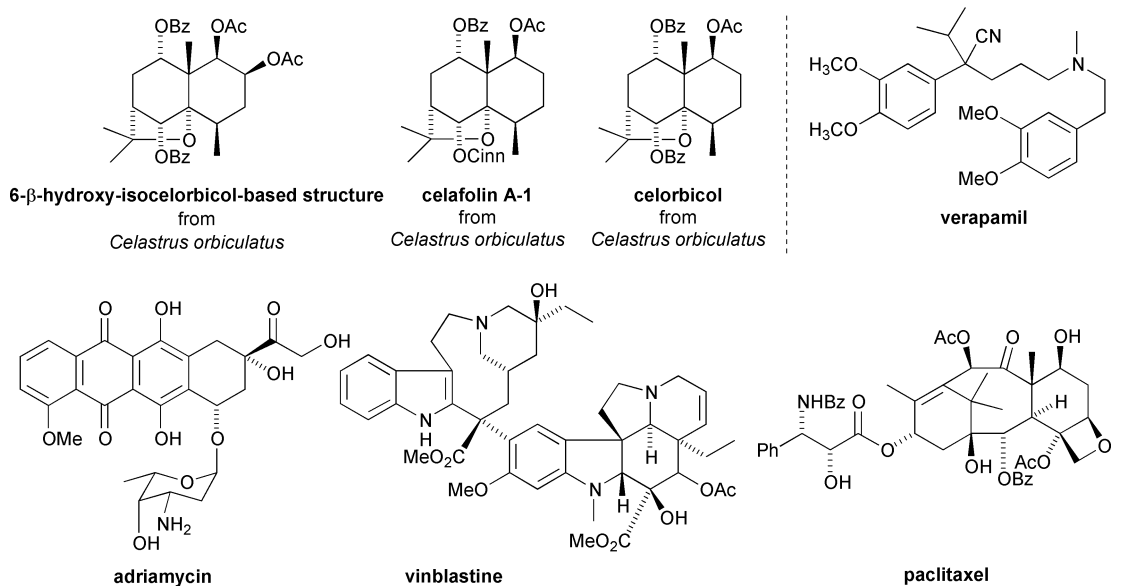


Fig. 13 MDR reversing sesquiterpenoids from *Celastrus orbiculatus* and the structures of MDR reversing agent verapamil and cancer chemotherapy agents adriamycin, vinblastine and paclitaxel.

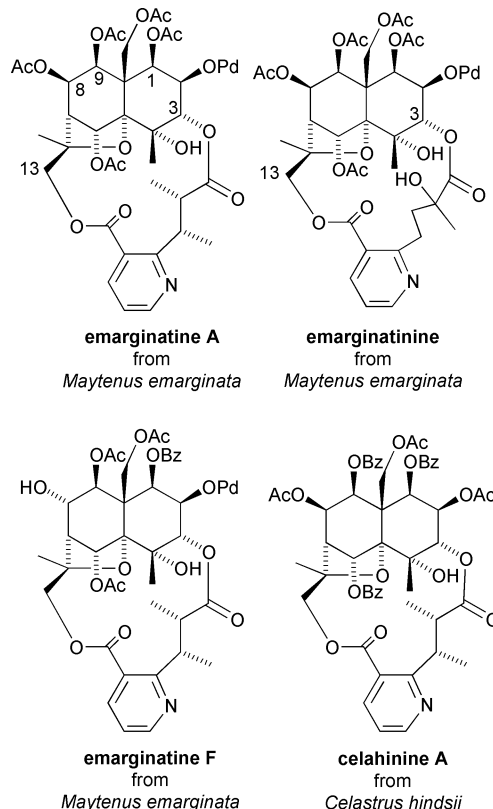


Fig. 12 Cytotoxic sesquiterpenoids from *Maytenus emarginata* and *Celastrus hindsii*.

MCF7/ADR.⁴³ These sesquiterpenoids were found to be less toxic and of greater reversing power than other known reversing agents such as verapamil that are currently approved for clinical use⁴² (Fig. 13).

More recently, a series of sesquiterpenoids based on 4β,14-dihydroxycelapanol and 3,13-dideoxyeuonyminol cores have been isolated from the aerial parts of *Crossopetalum tonduzzi* and *Maytenus macrocarpa*.⁴⁴ These have been found to reverse the resistance of parasitic protozoan *Leishmania tropica* to growth inhibition by daunomycin (75–95% at 15 μM concentration with respect to uninhibited control growth)⁴⁴ (Fig. 14).

The size of the substituent at C-2 was suggested to be important for MDR activity.⁴⁴ The most active compounds were

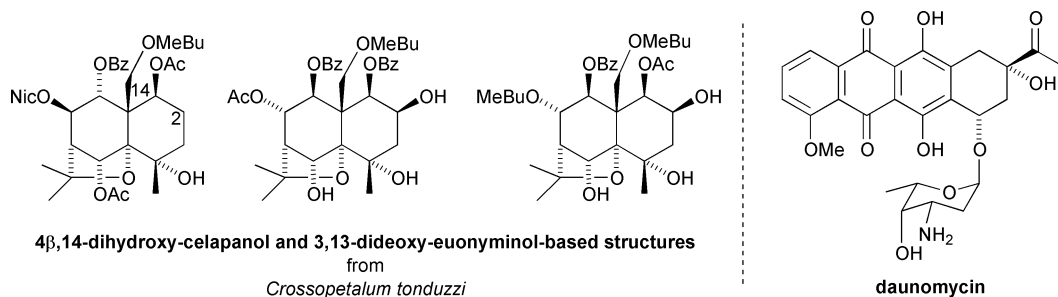


Fig. 14 MDR reversing sesquiterpenoids from *Crossopetalum tonduzzi* and the structure of cancer chemotherapy agent daunomycin.

those with a proton or alcohol substituent at C-2: esterification at this site resulted in reduced activity. In contrast, a benzoyl at C-1 imparted greater activity than an acetyl.⁴⁴

3.4 Immunosuppressive activity

Immunosuppressive agents are key components within the cocktail of drugs administered during organ transplant surgery.⁴⁵ Promising immunosuppressive activity has been reported for two sesquiterpenoid constituents, wilfortrine and euonine,⁴⁶ and a triterpene constituent, celastrol,⁴⁵ of *Tripterygium wilfordii*. The sesquiterpenoids are based on the euonyminol core, have C-3–C-13 hydroxywilfordic acid dilactone bridges, and have been found to elicit marked depressant effects on humoral-mediated immunity using the hemolysin reaction index on mice (wilfortrine, 40 mg kg⁻¹; euonine, 80 mg kg⁻¹).⁴⁶ Both sesquiterpenoids significantly decreased charcoal particle clearance and the weights of spleen and thymus in the mice relative to healthy control animals at 80 mg kg⁻¹ (Fig. 15).

3.5 Anti-HIV activity

Perhaps the most exciting biological activity associated with the Celastraceae sesquiterpenoids is that of selective anti-HIV activity. Takaishi has recently reported that various macrolactone containing dihydroagarofuran derivatives, and in particular, hypoglaunine B, triptonine B, and hyponine B extracted from the root bark of *Tripterygium hypoglaucum*, exhibit potent inhibition of HIV virus replication in human-

lymphocyte cells.¹⁵ All three sesquiterpenoids, and also wilfortrine (Fig. 16), display EC₅₀ values of <0.01 μg mL⁻¹ and *in vitro* therapeutic indexes (TIs)^{†††} >1000.¹⁵ In general a TI >5.0 is considered significant. By way of comparison clinically approved anti-HIV agent AZT has an EC₅₀ value of <0.012 μg mL⁻¹ and TI of ~42000 under these conditions.¹⁵

It is apparent from the foregoing, by no means exhaustive,²⁸ overview of biological activities associated with polyester dihydroagarofuran extracts of the Celastraceae that these intriguing compounds possess a rich and diverse spectrum of medicinally interesting activity. However, low natural abundance coupled with isolation difficulties continues to impede exhaustive biological screening and the establishment of meaningful structure–activity relationships for this class of natural products. Consequently, their molecular modes of action remain unknown. It is unlikely that this situation will be rectified unless robust and flexible asymmetric syntheses of the core structures are developed. This would pave the way for the total synthesis of selected fully esterified natural products and hopefully allow the identification of pharmacophore leads for drug development. However, synthetic endeavours in this area to date have been relatively scarce (see next section). This probably reflects the fact that many of these compounds have complex structures containing dense contiguous functionality and the lack of a single ‘high-profile’ target structure (*cf. e.g.* taxol) to attract synthetic chemists. Significant biological activity appears to encompass a plethora of stereochemical permutations around the dihydroagarofuran core.²⁸ However, it is striking that many of the most biologically active members of this class have a symmetric array of hydroxylation across the α-

||| The EC₅₀ is the effective concentration required to produce a 50% reduction in viral activity *in vivo*.

††† The TI is the ratio of IC₅₀ to EC₅₀, and is a measure of the selectivity for diseased cells over healthy cells.

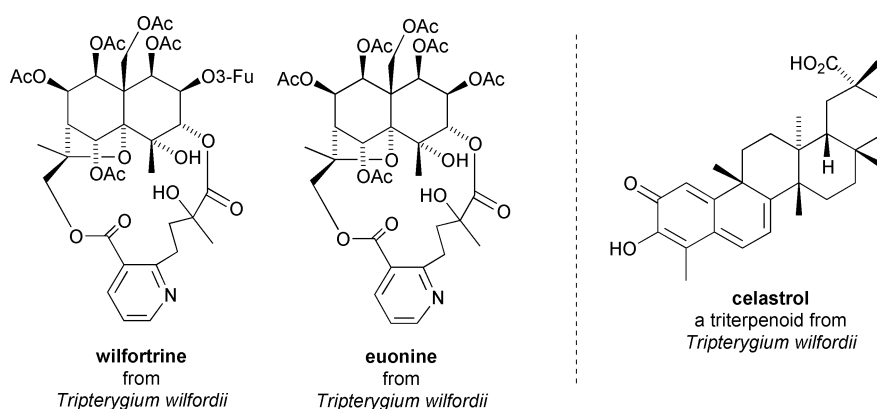


Fig. 15 Immunosuppressive sesquiterpenoids from *Tripterygium wilfordii* and the structure of immunosuppressive triterpene celastrol.

face of their northern periphery. It is hoped that this observation will inspire further efforts towards the synthesis of these intriguing compounds.

4 Synthetic approaches to Celastraceae sesquiterpenoids⁴⁷

4.1 Early synthetic work—syntheses of the agarofuran skeleton

The first agarofuran synthesis reported was that of (+)- α -agarofuran by Barrett and Büchi in 1967.⁴⁸ Their synthesis employed readily available (–)-10-epi- α -cyperone as starting material.††† The overall efficiency of their synthesis was, however, compromised by the formation of a mixture of triene isomers (**1** and **2**) early in the synthesis (only one of which underwent photooxygenation), and by a final dehydration step which afforded the undesired alkene isomer **5** as a major by-product. Of particular note in their synthesis was the facile alumina-catalysed cyclisation reaction of the axial C-5 tertiary alcohol of **3** onto C-11 of the axial isopropenyl double bond in **4** used to close the C-11–O bond of the tetrahydrofuran C-ring (Scheme 1).

Subsequently, Marshall and Pike reported a more efficient synthesis of (+)- α -agarofuran from (–)-10-epi- α -cyperone in a sequence of six steps.⁵⁰ In contrast to Barrett and Büchi these workers installed the tetrahydrofuran C-ring by C-5–O bond formation. Thus, cyclisation of the C-11 isopropene-derived tertiary alcohol onto the C-4–C-5 alkene (**6** \rightarrow **7**) was triggered by treatment with MCPBA, presumably *via* ring opening of an intermediate α -epoxide (which could not be detected). They

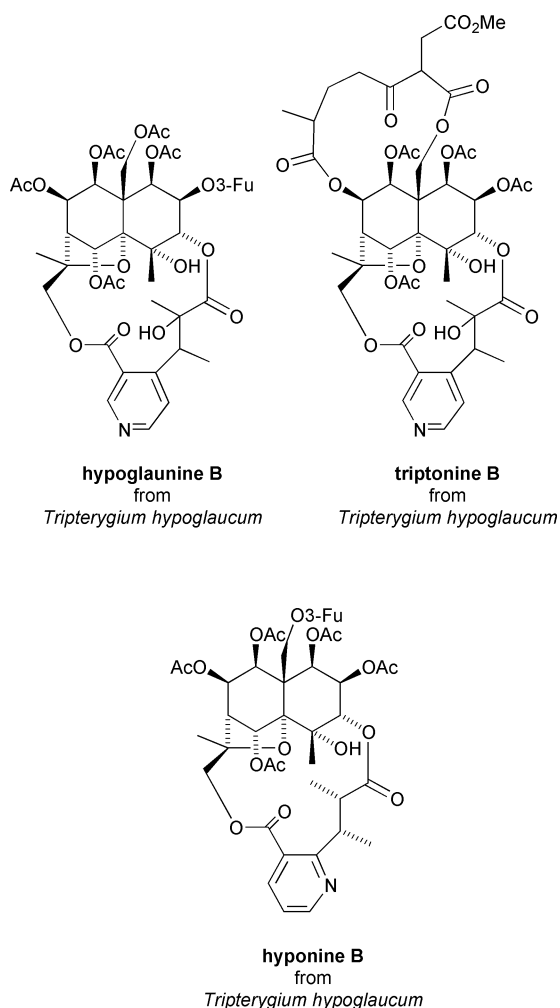
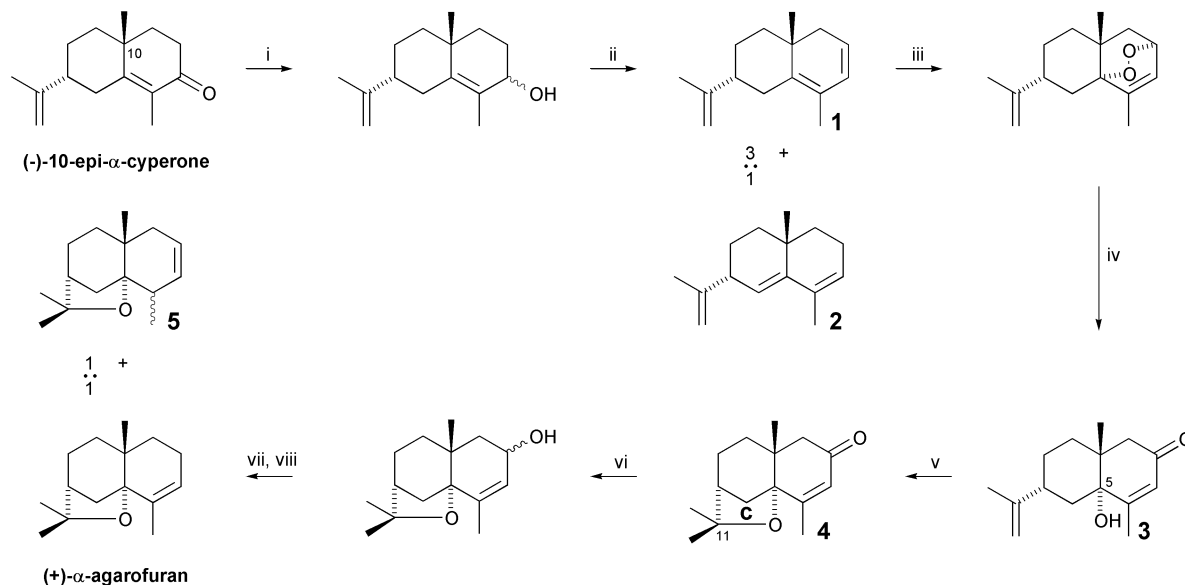
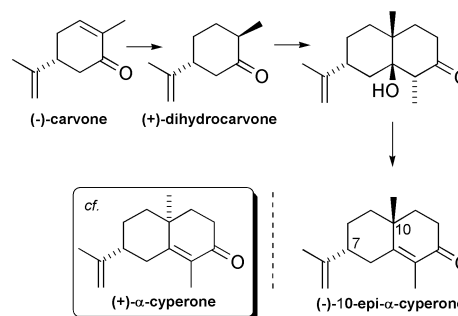


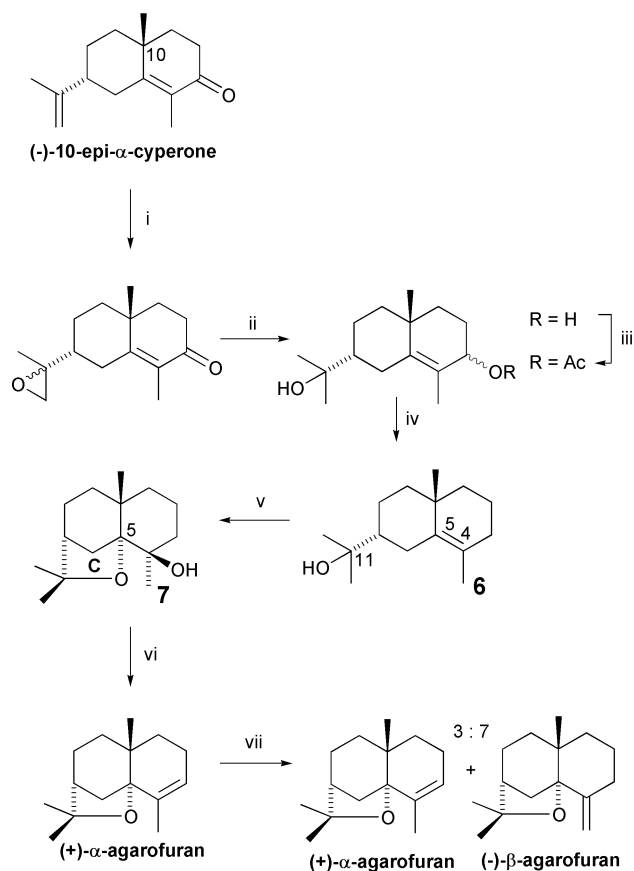
Fig. 16 Anti-HIV sesquiterpenoids from *Tripterygium hypoglaucum*.

††† (–)-10-Epi- α -cyperone has the same absolute stereochemistry at C-7 and C-10 as natural agarofurans. It can be prepared on a large scale in three steps from (–)-carvone by diastereoselective hydrogenation, Robinson annulation (then isomer separation), and dehydration in ~35% yield.⁴⁹



Scheme 1 The Büchi synthesis of (+)- α -agarofuran (1967). Reagents and yields: (i) LiAlH_4 [81%]; (ii) Al_2O_3 -Pyr [81%, total]; (iii) O_2 , $h\nu$ [62%]; (iv) basic Al_2O_3 [84%]; (v) acidic Al_2O_3 [72%]; (vi) NaBH_4 [88%]; (vii) SOCl_2 ; (viii) LiAlH_4 [87%, total].

also attempted to develop a method for the conversion of (+)- α -agarofuran to (-)- β -agarofuran. However, they found that irradiation of their product using a high-pressure Hg vapour lamp effected only partial photochemical isomerisation to a 3 : 7 mixture of α - and β -agarofurans⁵⁰ (Scheme 2).



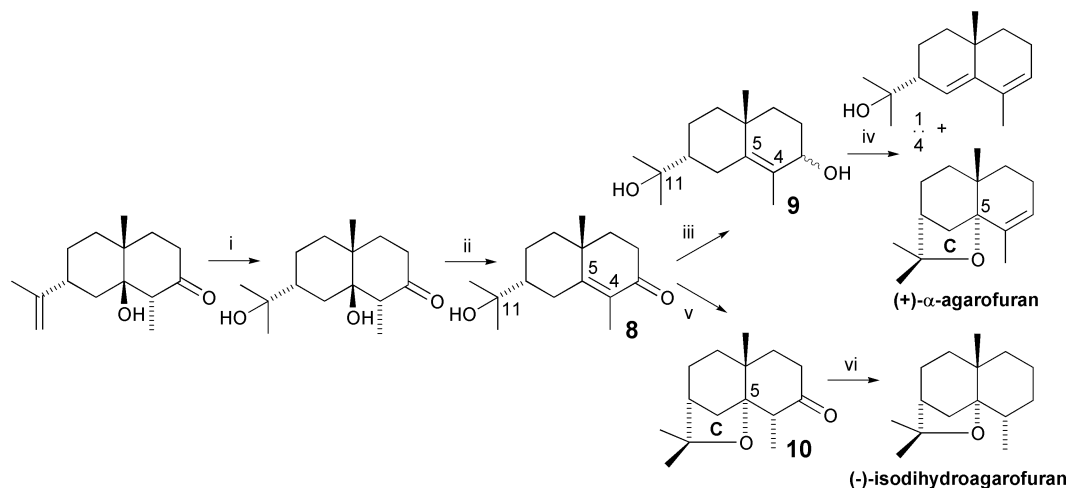
Scheme 2 The Marshall synthesis of (+)- α -agarofuran (1968). *Reagents and yields:* (i) MCPBA; (ii) LiAlH_4 ; (iii) Ac_2O ; (iv) Li , NH_3 [83%, 4 steps]; (v) MCPBA. [55%]; (vi) SOCl_2 [94%]; (vii) $h\nu$, xylene-IPA [100%, total].

A shorter synthesis of (+)- α -agarofuran was reported by Deslongchamps *et al.*⁵¹ using the dehydration precursor of (-)-10-epi- α -cyperone as starting material. In this synthesis, as in Marshall and Pike's, the tetrahydrofuran C-ring was installed by C-5-O bond formation [9 \rightarrow (+)- α -agarofuran]. In this case, however, the C-4-C-5 alkene formed part of an allylic alcohol system in **9**, and so cyclisation of the isopropene-derived C-11 tertiary alcohol could be effected by acid-

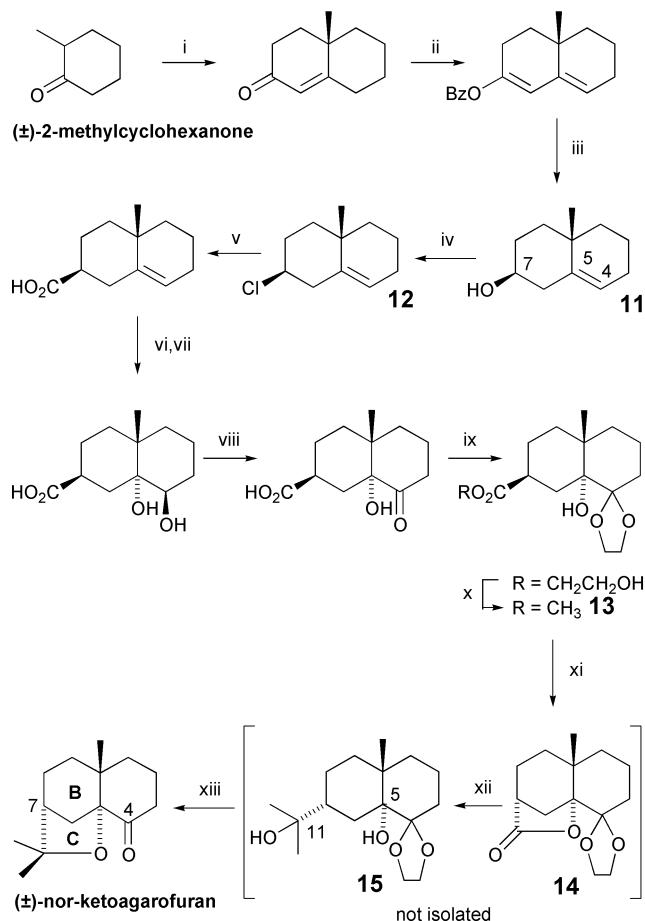
catalysed intramolecular substitution with allylic rearrangement. This ring-closure was high yielding, but the efficiency was compromised by the co-formation of an uncyclised diene. An analogous acid-catalysed ring-closure was also shown to be possible when the C-4-C-5 alkene formed part of an enone system (**8** \rightarrow **10**). Although this ring-closure reaction was considerably lower yielding it enabled the first synthesis of (-)-isodihydroagarofuran⁵¹ (Scheme 3).

In 1972 Kelly reported a diastereoselective route to (\pm)-nor-ketoagarofuran, which is an analogue of β -agarofuran having a C-4 ketone group in place of the C-4-C-15 alkene.⁵² The approach was an evolution of earlier endeavours by Heathcock and Kelly in which the final steps had turned out to be capricious and irreproducible.⁵³ Kelly employed an interesting epimerisation-lactonization strategy to install the key tetrahydrofuran C-ring, and as such this was the first synthesis of an agarofuran which did not rely on (-)-10-epi- α -cyperone for provision of the crucial axial stereochemistry at C-7 of the B-C-ring junction. The early stages of the synthesis featured an unusual conversion of the equatorial C-7 alcohol into the corresponding chloride using PCl_5 with retention of configuration as the result of neighbouring-group participation by the C-4-C-5 alkene (**11** \rightarrow **12**). Once this chloride was converted to the corresponding methyl ester, inversion of this centre was achieved by the ingenious base-mediated epimerisation step driven by lactonisation onto the axial C-5 tertiary alcohol and removal of methanol (**13** \rightarrow **14**). Conversion of lactone **14** into the corresponding dimethyl tetrahydrofuran C-ring involved treatment with MeLi followed by acid-catalysed ring-closure of the resulting C-11-C-5 diol [15 \rightarrow (\pm)-nor-ketoagarofuran]⁵² (Scheme 4).

The first stereocontrolled synthesis of (-)- β -agarofuran was reported by Büchi and Wüest in 1979.¹⁸ Their synthesis employed (-)-carvone as starting material and was unusual in that the tetrahydrofuran C-ring was installed relatively early in the sequence. Thus, C-11-O bond formation was achieved by intramolecular 1,2-addition of the isopropene-derived C-11 tertiary alcohol to a C-5 ketone upon treatment with PCl_5 (**16** \rightarrow **17**). This set the stage for the penultimate step, an elegant radical cyclisation of the A-ring with concomitant installation of a C-4-C-15 vinylsilane as a mixture of stereoisomers (**17** \rightarrow **18**). This inseparable mixture of vinylsilanes was readily converted into the requisite exomethylene function of (-)- β -agarofuran on treatment with acid [**18** \rightarrow (-)- β -agarofuran]. A further important discovery by these workers was that (-)- β -agarofuran could be hydrogenated with >95:5 diastereoselectivity to (-)-dihydroagarofuran using diimide (*cf.* standard catalytic hydrogenation which is much less selective). Pre-coordination of the diimide to the tetrahydrofuran ether oxygen



Scheme 3 The Deslongchamps synthesis of (+)- α -agarofuran (1968). *Reagents and yields:* (i) $\text{Hg}(\text{OAc})_2$, NaOH , NaBH_4 [75%]; (ii) NaOMe [81%]; (iii) $\text{LiAl}(\text{O}^t\text{Bu})_3\text{H}$ [100%]; (iv) PTSA [100%, total]; (v) PTSA [30%]; (vi) toluene-*p*-sulfonylhydrazine, then NaBH_4 [25%].



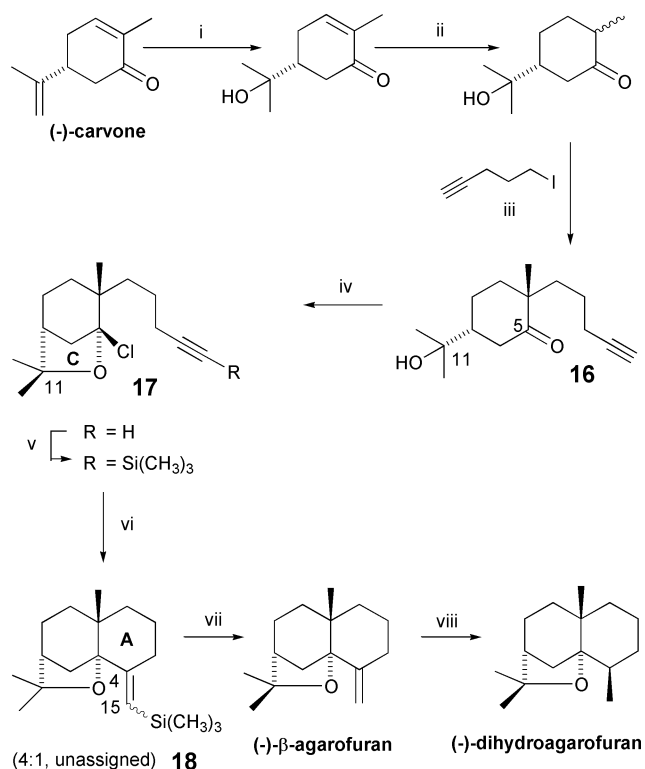
Scheme 4 The Kelly synthesis of (±)-nor-ketoagarofuran (1972). *Reagents and yields:* (i) Na, MeCOCH₂CH₂NEt₂ [35%]; (ii) BzCl; (iii) NaBH₄ [60%, 2 steps]; (iv) PCl₅ [72%]; (v) Mg then CO₂ [78%]; (vi) HCO₂H–H₂O₂; (vii) NaOH [50%, 2 steps]; (viii) Jones' reagent [93%]; (ix) PTSA, HO-(CH₂)₂OH [42%]; (x) LiOMe–BzOEt, MeOH [70%]; (xi) LiOMe–BzOEt, dioxane (xii) MeLi; (xiii) HCl [65%, 3 steps].

was implicated as being responsible for the high selectivity¹⁸ (Scheme 5).

4.2 Synthetic approaches to polyoxygenated agarofurans

Following these pioneering efforts by the groups of Büchi, Marshall, Deslongchamps, and Kelly, the late 1970s and early 1980s saw Huffmann *et al.* take up the challenge of developing these foundations into an approach to the more highly oxygenated agarofuran derivatives found in the Celastraceae. After a number of twists and turns, this work culminated in the total synthesis of (±)-isocolorbicol in 1987.²² Huffmann's final approach to (±)-isocolorbicol began with a three-step synthesis of (±)-10-epi-9-oxo-α-cyperone from (–)-carvone *via* (±)-hydroxycarvone. §§§ This sequence featured a Robinson annulation reaction analogous to the one used for the formation of (–)-10-epi-α-cyperone from (+)-dihydrocarvone. ††† (±)-10-Epi-α-cyperone was converted into 9-keto-α-agarofuran by a method closely similar to that used in the 9-deoxy series by Deslongchamps *et al.*, but employing Jones' reagent to effect the C-11–O bond formation for tetrahydrofuran C-ring formation (19 → 20). The remainder of the synthesis proceeded with high levels of stereocontrol and featured a diimide reduction of the C-4–C-15 alkene in the manner of Büchi's β-agarofuran synthesis (21 → 22) and a totally diastereoselective dihydroxylation of the C-1–C-2 alkene on the α-face using stoichio-

§§§ Racemisation accompanies conversion of (–)-carvone into (±)-hydroxycarvone because the 1,3-diketo tautomer of (±)-hydroxycarvone is achiral.



Scheme 5 The Büchi synthesis of (–)-β-agarofuran (1979). *Reagents and yields:* (i) aq. H₂SO₄ [63%]; (ii) 10% Pd/C–H₂ [93%]; (iii) KNH₂ [41%]; (iv) PCl₅ [71%]; (v) EtMgBr then TMSCl [98%]; (vi) AIBN, HSnBu₃, *hv* [72%, total]; (vii) PTSA [92%]; (viii) hydrazine, H₂O₂ [92%].

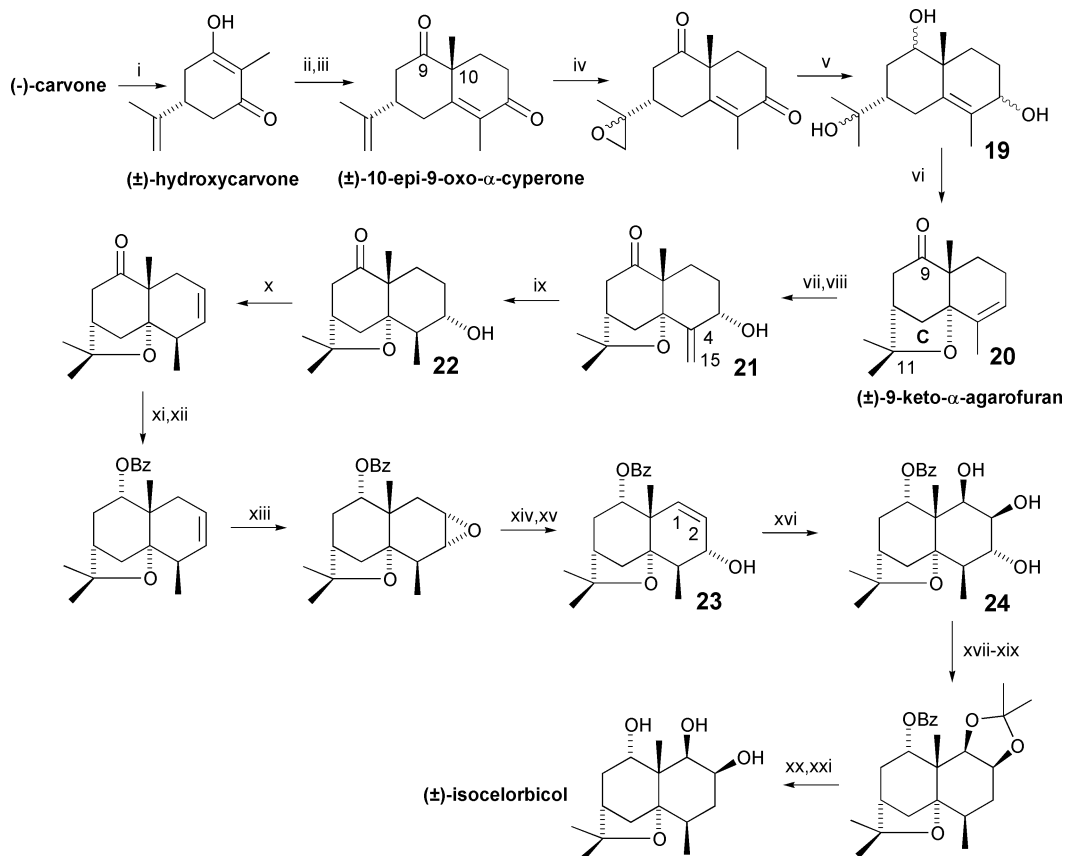
metric OsO₄ (23 → 24). The overall yield of (±)-isocolorbicol over the fifteen steps from 9-keto-α-agarofuran was 3.2% (Scheme 6).

No significant further developments were made towards the synthesis of more highly oxygenated dihydroagarofurans until the early 1990s. At this time two Chinese groups began to report a series of detailed studies towards the synthesis of functionalised agarofurans. The groups of Li⁵⁴ and Guo⁵⁵ have now developed a number of modifications and extensions to the syntheses described above, from (–)-carvone and (±)-hydroxycarvone, so as to access oxygenated agarofuran derivatives containing up to three additional oxygen functions (Scheme 7).

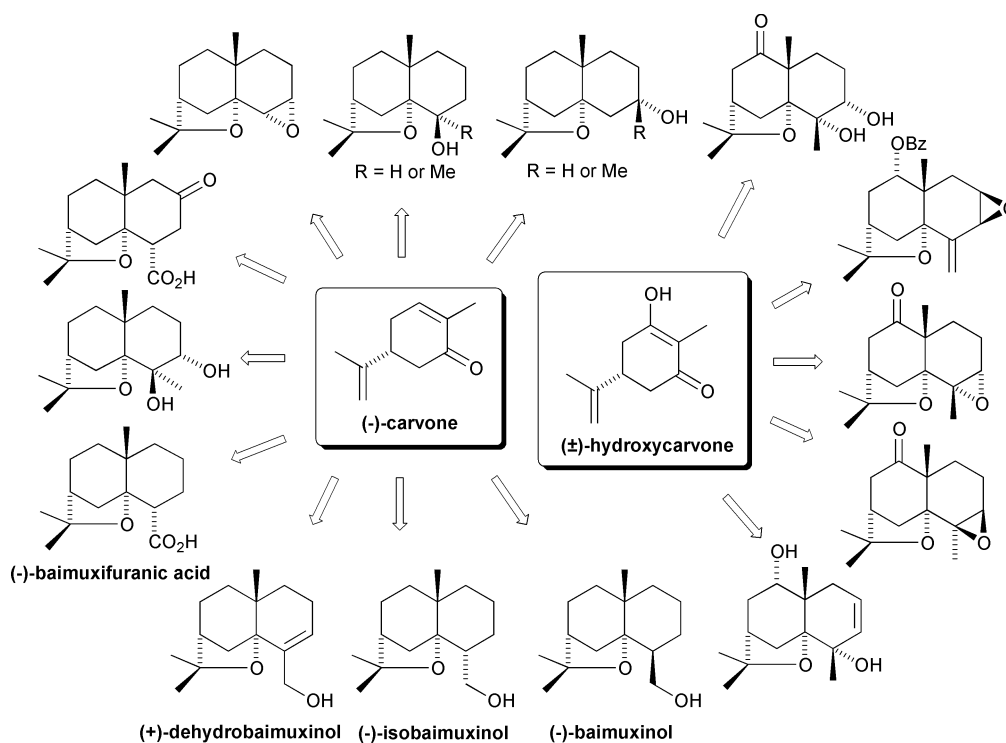
Of particular note from this corpus of work was Li's optimisation of Huffmann's (+)-α-agarofuran and (±)-9-keto-α-agarofuran syntheses by rendering the Robinson annulation reactions more diastereoselective and improving the C-11–O bond formation for tetrahydrofuran C-ring cyclisation by the use of H₂SO₄ in place of Jones' reagent.⁴⁹ Additionally, Li has employed the Shapiro reaction^{¶¶¶} to convert the tosyl hydrazone of 3-keto-4β,9β-dihydroxydihydroagarofuran 25 into the corresponding 2,3-unsaturated compound 26 in an approach towards 1α,9β-dibenzoyloxy-2β,3β,4β-trihydroxydihydroagarofuran 27.^{56–58} This target compound is a natural product from *Salvia palaefolia*s which is used in Colombia as an anti-hypertensive agent⁵⁸ (Scheme 8).

More recently, the group of Tu⁵⁹ has explored the use of the readily available sesquiterpene (–)-α-santonin as a conveniently functionalised starting material for the synthesis of

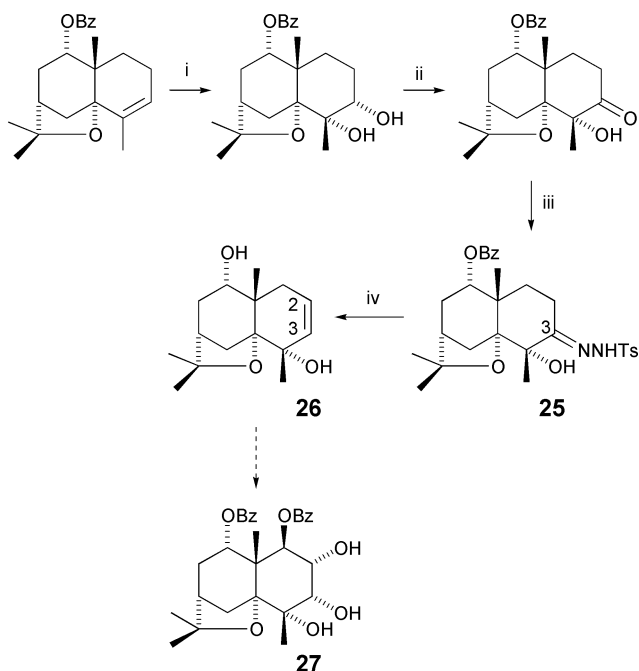
¶¶¶ Both the Shapiro (LDA) and Bamford–Stevens (Na, HOCH₂CH₂OH) conditions have been used previously on related tosylhydrazonyl decalins lacking a hydroxy group at C-4 to give alkenes. The Shapiro conditions give the 2,3-alkene⁵⁶ whereas the Bamford–Stevens conditions give the 3,4-alkene.⁵⁷



Scheme 6 The Huffmann synthesis of (±)-isocolorbicol (1986). *Reagents and yields:* (i) KOH–H₂O₂ then HCl [60%]; (ii) EVK, KOH; (iii) PTSA [32%, 2 steps]; (iv) MCPBA; (v) LiAlH₄; (vi) Jones' reagent [47%, 3 steps]; (vii) MCPBA, NaHCO₃ [70%]; (viii) LDA [72%]; (ix) NH₂NH₂, NaIO₄, CuSO₄, AcOH [90%]; (x) POCl₃ [65%]; (xi) LiAlH₄; (xii) BuLi then BzCl [93%, 2 steps]; (xiii) MCPBA [60%]; (xiv) (PhSe)₂, NaBH₄ [44%]; (xv) MCPBA, ^tPr₂NH [87%]; (xvi) OsO₄, Pyr [66%]; (xvii) 2,2-DMP, CSA [87%]; (xviii) NaH, imidazole then CS₂ then MeI; (xix) ⁿBu₃SnH [82%, 2 steps]; (xx) Ba(OH)₂; (xxi) HCl [86%, 2 steps].



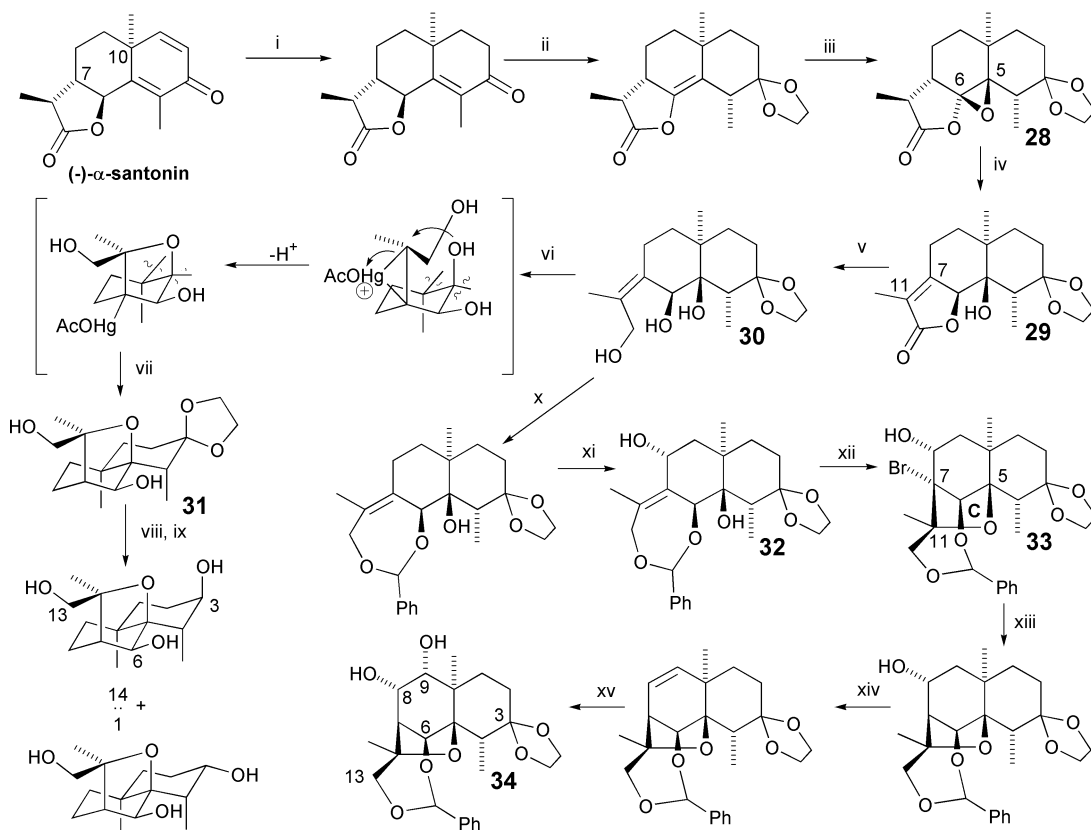
Scheme 7 Overview of the Li and Guo syntheses of oxygenated agarfurans (1990s).



Scheme 8 The Li synthesis of (\pm) -2,3-dehydro-4 β ,9 β -dihydroxydihydroagarofuran (1995). *Reagents and yields:* (i) OsO₄, Pyr [99%]; (ii) DMSO, TFAA, Et₃N [75%]; (iii) TsNHNH₂ [100%]; (iv) LDA [70%].

oxygenated dihydroagarofurans. Of particular interest from these studies is that, in contrast to all the approaches mentioned

(–)- α -Santonin has the absolute configuration depicted in Scheme 9 in which C-10 is epimeric to that required for naturally occurring agarofurans. Consequently, Tu's products are in the opposite enantiomeric series to that of the natural products. This is clear from the conversion of (–)- α -santonin into (+)- α -cyperone (*cf.* footnote †††).⁶⁰



Scheme 9 The Tu approach to dihydroagarofurans from (–)- α -santonin (1998, 1999). *Reagents and yields:* (i) H₂, Raney-Ni [80%]; (ii) PTSA, HO(CH₂)₂OH [66%]; (iii) MCPBA [68%]; (iv) NaOMe [83%]; (v) LiAlH₄ [95%]; (vi) Hg(OAc)₂; (vii) NaBH₄ [82%, 2 steps]; (viii) PTSA, acetone; (ix) LiAlH₄ [70%, 2 steps]; (x) PhCHO, ZnCl₂ [72%]; (xi) SeO₂, ^tBuOOH [82%]; (xii) NBS, CaCO₃ [95%]; (xiii) ^tBu₃SnH [92%]; (xiv) SOCl₂, Pyr [52%]; (xv) NMO, OsO₄ [87%].

above, the use of this starting material allows differentiation of the C-12 and C-13 substituents of the tetrahydrofuran C-ring. This is required for the synthesis of the most highly oxygenated Celastraceae target cores (*e.g.* euonyminol and evoninol, see Fig. 4) which have C-12 as a methyl group and C-13 as a hydroxymethyl group. The orchestration of synthetic steps that allowed for this differentiation started with an unusual rearrangement of the C-5–C-6 epoxy lactone **28** to the C-7–C-11 alkenyl lactone **29** on treatment with NaOMe. This transformation collapses the C-7 stereocentre (which held the C-7–C-11 lactone bond in the undesirable equatorial orientation in **28**) to give the tetrasubstituted C-7–C-11 alkene in **29** with complete stereoselectivity. At a later stage, a rather neat cyclisation of the axial C-5 tertiary alcohol onto the *Si*-face of this alkene at C-11 is employed to close the C-11–O bond of the agarofuranyl tetrahydrofuran C-ring. This cyclisation sets up the correct axial configuration at C-7 and establishes C-12 and C-13 as methyl and hydroxymethyl groups, respectively. Initial studies used a mercuric acetate-mediated ring-closure reaction followed by reductive demercuration for this purpose (**30** → **31**),⁶¹ but subsequently a cleaner NBS-mediated ring-closure protocol, followed by ⁿBu₃SnH-mediated dehalogenation was disclosed (**32** → **33**).⁶² This method was used for the preparation of their most advanced intermediate to date: the 3-keto-6,8,9,13-tetrahydroxyagarofuran derivative **34**⁵⁹ (Scheme 9).

Notwithstanding the important contributions made by the aforementioned groups, the most significant synthesis in the Celastraceae sesquiterpenoid area has undoubtedly been White *et al.*'s synthesis of (\pm) -euonyminol in 1997.²⁰ This synthesis opened with a Diels–Alder reaction between an *in situ* prepared benzoquinone and a siloxypentadiene which established the basic decalin A–B ring system **35**. The crucial axial stereochemistry at C-7 of the B–C ring junction was established by an unusual conjugate addition reaction of ⁷PrMgBr to the β -face of the B-ring enone directed by coordination to the C-6 hydroxy

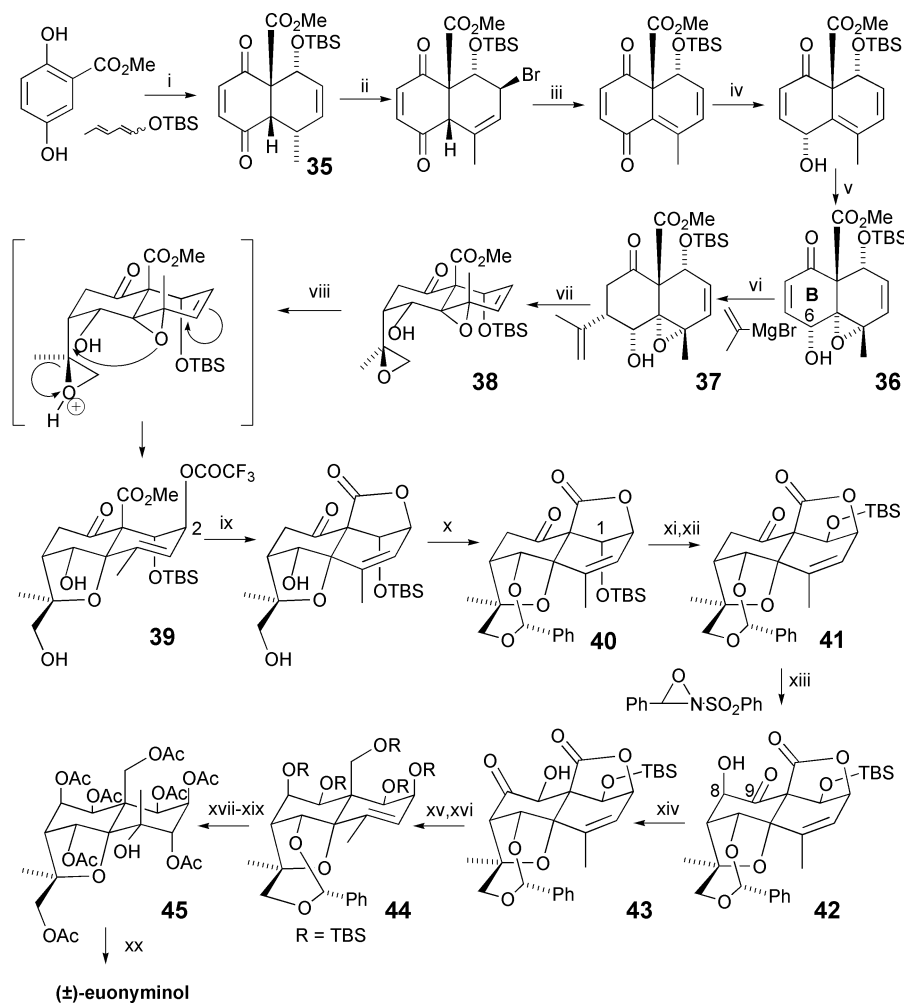
group (**36** → **37**). Subsequent epoxidation of the isopropenyl double bond (**37** → **38**),^{††††} again directed by the proximal C-6 hydroxy group, set the stage for an impressive acid-mediated cascade reaction. This cascade reaction (**38** → **39**), which formed the cornerstone of White's synthesis, not only closed the tetrahydrofuran C-ring by C-11–O bond formation, it also established C-12 and C-13 as methyl and hydroxymethyl, respectively, and installed oxygenation at C-2 with the correct α -orientation. Elaboration of the cascade product **39** into the highly oxygenated (\pm)-euonyminol Celastraceae core was achieved, generally with high levels of stereocontrol, by a further series of elegant steps. Particular highlights included an aldol-retro-aldol reaction sequence to invert the C-1 hydroxy substituent (**40** → **41**) and the use of a Me_3Al -mediated Lobry de Bruyn–Alberda van Eckenstein rearrangement to accomplish 1, 2-transposition of the C-8–C-9 vicinal hydroxyketone (**42** → **43**). Although initial attempts to effect the final *cis*-dihydroxylation of the C-3–C-4 alkene lacked stereocontrol, a change of protecting group regime to that shown in Scheme 10 (*i.e.* **44** → **45**) resulted in almost exclusive β -face attack as required.²⁰

Very recently Ducrot *et al.* have described the synthesis of various racemic functionalised decalins designed to be advanced intermediates for the preparation of polyhydroxylated Celastraceae sesquiterpenoid cores.⁶³ The synthesis of the most

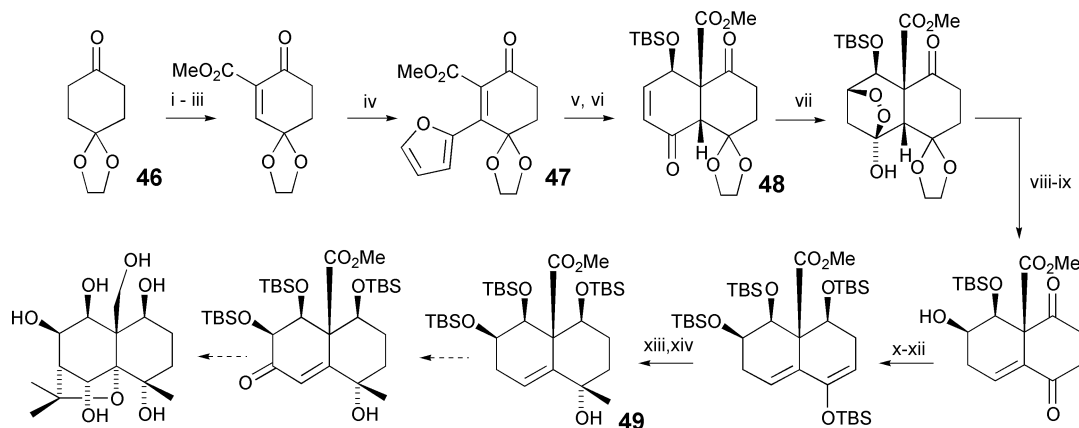
elaborate intermediate **49** uses the cyclohexane-1,4-dione derivative **46** as starting material. This is converted to a conveniently functionalised decalin enone **48** in a series of six steps featuring a neat oxidative cleavage of a furan ring with concomitant intra-molecular aldol condensation (**47** → **48**) (Scheme 11).

Ducrot *et al.* have also disclosed some model studies for tetrahydrofuran C-ring closure of potential utility later in their synthesis.⁶⁴ Essentially two strategies were explored for conversion of the B-ring enone functionality of readily available (\pm)-Wieland–Miescher ketone into the B–C-ring junction of an agarofuran. The first method proceeded *via* the *trans*-decalin vinyl nitrile **50** and afforded the simple ring-closed agarofuran **55**, whereas the second method proceeded *via* the *cis*-decalin vinyl nitrile **51** and also introduced a β -hydroxy group at C-6 to give agarofuran **57**, albeit in substantially lower yield.⁶⁴ Both methods bore similarities to the Kelly approach to tetrahydrofuran C-ring-closure (*cf.* Scheme 4). Thus, the first method exploited a base-mediated α - to β -face epimerisation of a C-7 aldehyde substituent driven by lactol formation (**52** → **53**), followed by aqueous H_2SO_4 -mediated ring-closure of the C-11–C-5 diol **54** to form the tetrahydrofuran C-ring in agarofuran **55**. In the second method analogous ring-closure of the C-11–C-5 diol **56** to form the tetrahydrofuran C-ring in agarofuran **57** was orchestrated to be accompanied by ring-opening of the C-6–C-7 α -epoxide by water thereby concomitantly introducing the C-6 β -hydroxy group (along with an unwanted tertiary α -hydroxy group at C-7)⁶⁴ (Scheme 12).

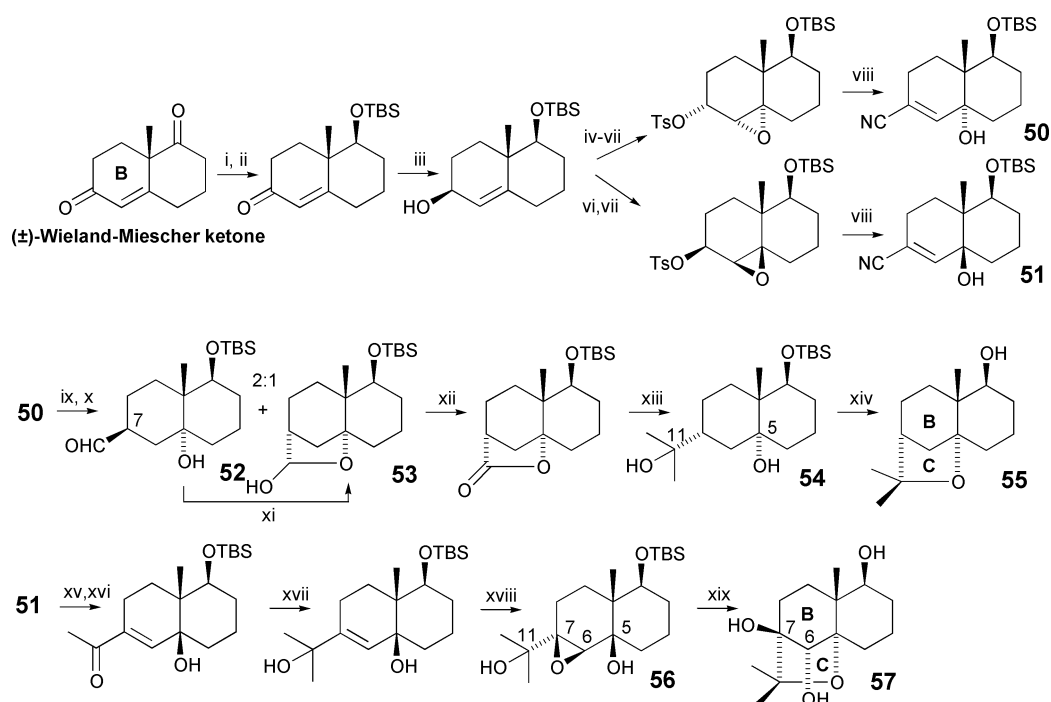
^{††††} It should be noted that in their publications White *et al.*²⁰ employ the reverse definitions of α -/ β -faces and A-/B-rings relative to the those employed here (*i.e.* as defined in Fig. 3).



Scheme 10 The White synthesis of (\pm)-euonyminol (1997). *Reagents and yields:* (i) Ag_2O [94%]; (ii) NBS, Bz_2O_2 ; (iii) Et_3N [98%, 2 steps]; (iv) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ [90%]; (v) MCPBA [88%]; (vi) LDA, 15-crown-5 [63%]; (vii) $t\text{BuOOH}$, 2,6-lutidine, $\text{VO}(\text{acac})_2$ [74%]; (viii) TFA; (ix) Pyr–THF– H_2O then imidazole, MeCN [75%, 2 steps]; (x) PPTS, $\text{PhCH}(\text{OMe})_2$ [83%]; (xi) $t\text{Bu}_4\text{NF}$ [96%]; (xii) TBSOTf, Et_3N [100%]; (xiii) KHMDS [86%]; (xiv) AlMe_3 [100%]; (xv) LiAlH_4 then HCl; (xvi) TBSOTf, Et_3N ; (xvii) OsO_4 , Pyr; (xviii) Amberlite IR-120, $\text{AcOH-H}_2\text{O}$; (xix) Ac_2O , Pyr, [30%, 5 steps]; (xx) NaOMe , MeOH, then Amberlite IR-120 [100%].



Scheme 11 The Ducrot synthesis of a functionalised (±)-decalin derivative (1999). *Reagents and yields:* (i) NaH, CO(OMe)₂; (ii) PhSeCl, Pyr; (iii) H₂O₂ [66%, 3 steps]; (iv) furan, BF₃ [61%]; (v) DMDO; (vi) TBSOTf, 2,6-lutidine [72%, 2 steps]; (vii) H₂O₂, NaOH [77%]; (viii) LiAlH₄ [56%]; (ix) PTSA [40%]; (x) TBSOTf, 2,6-lutidine; (xi) LiBH₄; (xii) TBSOTf, 2,6-lutidine; (xiii) TFA [94%, 4 steps]; (xiv) MeLi [36%].



Scheme 12 The Ducrot strategy for tetrahydrofuran ring-closure (2000). *Reagents and yields:* (i) NaBH₄ [98%]; (ii) TBSCl, imidazole [92%]; (iii) DIBAL-H [97%]; (iv) (NO₂)₂C₆H₃CO₂H, DEAD, PPh₃; (v) K₂CO₃ [75%, 2 steps]; (vi) MCPBA [51%, 2 steps]; (vii) TsCl, Pyr [82%]; (viii) NaCN, HMPA [79%]; (ix) 10% Pd/C, H₂ [80%]; (x) DIBAL-H [42%, total]; (xi) Al₂O₃ (basic) [100%]; (xii) Ag₂CO₃, Celite [72%]; (xiii) MeLi [68%]; (xiv) H₂SO₄, acetone [65%]; (xv) MeLi; (xvi) PPTS [75%, 2 steps]; (xvii) MeLi [80%]; (xviii) MCPBA [91%]; (xix) H₂SO₄ [39%].

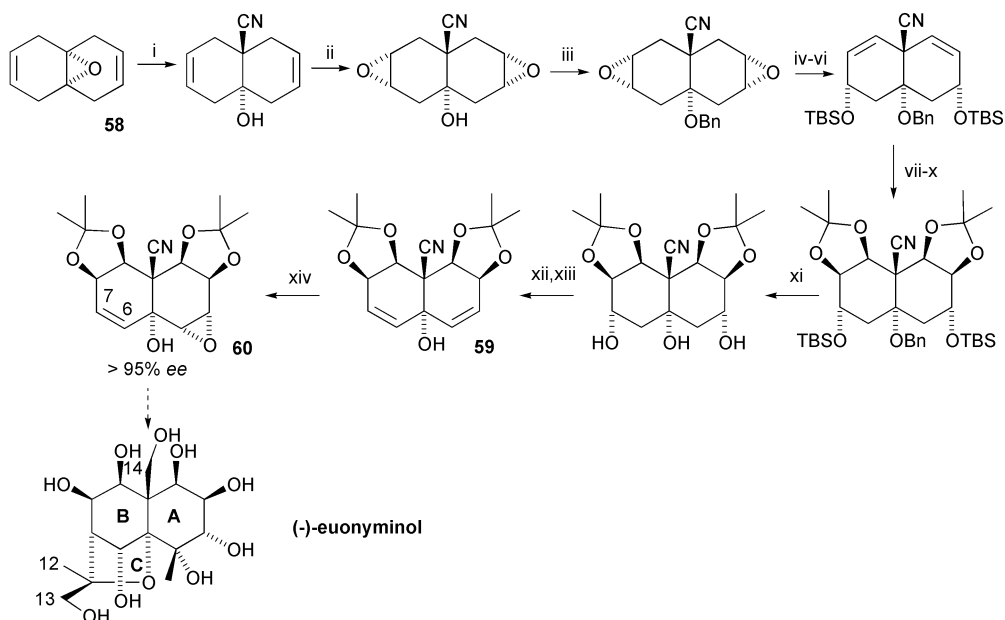
Our own approach to the synthesis of Celastraceae cores having symmetric oxygenation patterns across the northern periphery of the α -face of the dihydroagarofuran ring system (e.g. 14-deoxyalatalol, alatalol, 4 β -hydroxyalatalol, and euonyminol, see Fig. 4) centres around a ‘late-stage’ enantioselective desymmetrisation of *meso*-decalin diallylic alcohol **59**.⁶⁵ It is the first approach yet described towards this class of natural product core by asymmetric synthesis. The starting epoxide **58** was readily prepared from naphthalene by Birch reduction then epoxidation. This epoxide **58** was then converted in a series of totally diastereoselective transformations in a two-directional fashion through to the key *meso*-diallylic alcohol **59**. Enantioselective desymmetrisation of this diallylic alcohol was then effected using a novel Zr-modified Sharpless asymmetric epoxidation protocol which afforded the desymmetrised epoxy alcohol **60**, containing eight contiguous chiral centres, in >95% ee⁶⁵ (Scheme 13).

We are currently exploring novel strategies for elaboration of the C-6–C-7 alkene in decalin **60** to allow tetrahydrofuran C-ring formation with concomitant differentiation of C-12 and C-

13, and introduction of a β -hydroxy group at C-6, as required for the preparation of (–)-euonyminol and (–)-evoninol.

5 Concluding remarks and outlook

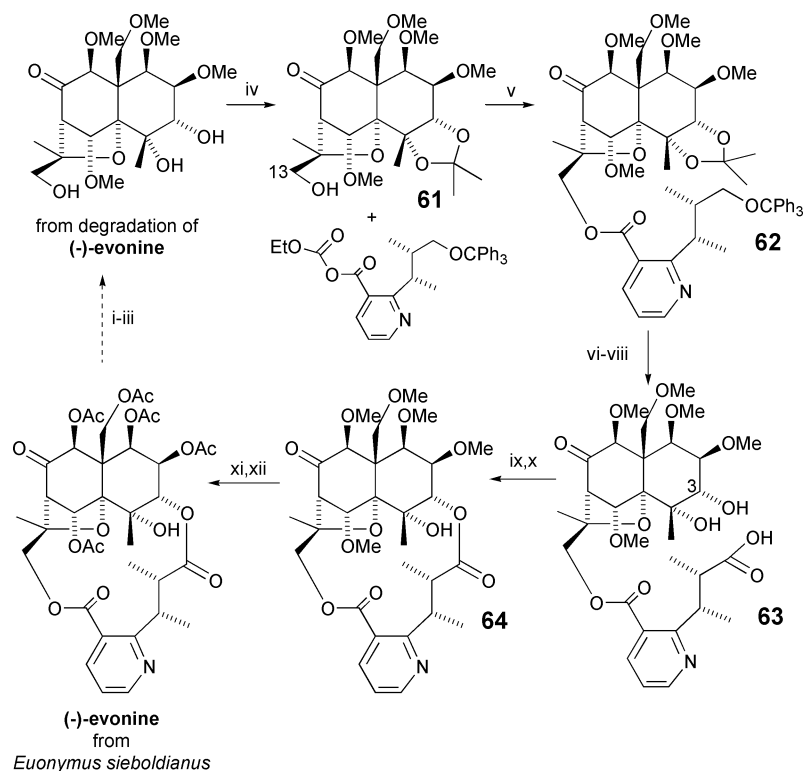
It is hoped that the foregoing overview of synthetic work towards the synthesis of Celastraceae sesquiterpenoid natural products will provide a stimulus for further synthetic work in this area. Many challenges remain to be met, and in particular there remains the formidable task, over and above that of synthesis of the appropriate core structures, of devising appropriate strategies for the elaboration of naturally occurring esterification patterns around the periphery of these molecules. The architectural complexity presented, particularly by the macrodilactone-containing structures such as hypoglaunine B (Fig. 16), will undoubtedly require meticulous planning and judicious use of orthogonal protecting groups for success. To date there has been limited synthetic work carried out on the preparation of the functionalised nicotinate diacids (cf. Fig. 5)⁶⁶ which constitute the backbone of many of these appendages^{1,4}



Scheme 13 The Spivey asymmetric synthesis of a functionalised decalin derivative (2001). *Reagents and yields:* (i) Et_2AlCN [98%]; (ii) $\text{VO}(\text{acac})_2$, $t\text{-BuOOH}$ [87%]; (iii) BnBr , NaH , $n\text{-Bu}_4\text{NI}$ [83%]; (iv) Ph_3PBr_2 [87%]; (v) TBSOTf , 2,6-lutidine [98%]; (vi) DBU [98%]; (vii) OsO_4 , NMO [79%]; (viii) PTSA , DMP [95%]; (ix) $\text{K}_2\text{OsO}_2(\text{OH})_4$, $\text{K}_3\text{Fe}(\text{CN})_6$, K_2CO_3 , MeSO_2NH_2 , quinuclidine [74%]; (x) PTSA , DMP [98%]; (xi) Na-NH_3 then TBAF [91%]; (xii) MsCl , Et_3N [99%]; (xiii) DBN [67%]; (xiv) $\text{Zr}(\text{O}^i\text{Pr})_4$, $i\text{-PrOH}$, D -(-)- DIPT , $t\text{-BuOOH}$ [55%].

and just one study relating to macrolactone synthesis.²³ This latter work was carried out by Yamada *et al.*²³ who in 1975 performed a re-synthesis of (–)-evonine from a triol derivative of (–)-evoninol obtained from degradation studies. Stepwise formation of the 14-membered dilactone ring was accomplished by ester formation at the C-13 hydroxy group (**61** → **62**) followed by macrolactonisation onto the C-3 hydroxy group [**63** → **64**] (Scheme 14).

Clearly there remains much challenging synthetic chemistry to be developed in order to provide compounds for biological screening. Impressive progress has, however, already been made and hopefully it will not be too long before synthetic material will be available to help unravel the biological modes of action of these molecules. Perhaps ultimately we may also be in a position to understand why nature defies entropy to create all these beautiful structures.



Scheme 14 The Yamada re-synthesis of evonine (1975). *Reagents and yields:* (i) NaOMe [67%]; (ii) MeI , NaH [75%]; (iii) NaOMe [84%]; (iv) $(\text{MeO})_2\text{CMe}_2$, CSA [56%]; (v) DMAP , Et_3N , DME [34%]; (vi) 80% AcOH [82%]; (vii) CrO_3 , Pyr [70%]; (viii) AcOH [68%]; (ix) CH_2N_2 ; (x) NaH , DMF [12%, 2 steps]; (xi) BCl_3 ; (xii) Ac_2O , Pyr [35%, 2 steps].

Note added in proof

Very recently Li *et al.* have published an asymmetric synthesis of (–)-isocelorbicol.⁶⁷

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