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Advances in the Synthesis of Aryltetralin Lignan Lactones

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Etoposide and tenoposide, derivatives of the aryltetralin lignan lactone podophyllotoxin (**5**), are clinically important anticancer agents. The structure of podophyllotoxin includes four contiguous chiral centres contained within a stereochemically unstable *trans*-fused tetrahydronaphthalene lactone skeleton. Reflecting this challenging structure and important biological role there has been long-standing interest in developing efficient stereocontrolled syntheses of this class of natural product. This microreview summarises the key developments towards this end focussing on more recent developments both from within the authors group and elsewhere.

1. Introduction

The lignans are a large family of secondary metabolites widely encountered in the plant kingdom.[1,2] The term lignan was first introduced by Harworth[3] in 1942 to describe a group of plant phenols whose general structure was determined by the union of two cinnamic acid residues linked via a β,β′ bond (Figure 1).

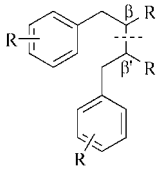

Figure 1. General structure of lignans.

Within this large family of lignans are the aryltetralin lignans **1** and **2** and aryltetralin lignan lactones **3**–**5** (Figure 2), which have long been recognised as particularly important natural products. To date, several hundred of these lignans have been isolated. Whilst their biological role in plants is unclear and remains to be fully elucidated, they have been shown to display a substantial range of biological activity and have a long and fascinating medical history that emanates from their use as folk remedies to treat an assortment of conditions.[4]

Structurally, these natural products are characterised by a substituted 1,2,3,4-tetrahydronaphthalene core. The aryltetralin lignan lactones contain an aryl unit at position 1 and a butyrolactone ring fused to positions 2 and 3 of the

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Jonathan Sellars was born in Doncaster, South Yorkshire, and received his undergraduate M. Chem. degree in Chemistry with Medicinal Chemistry from Huddersfield University in 2003. He then joined the group of Patrick Steel at the University of Durham to undertake a Ph. D. developing new synthetic chemistry using silenes, compounds with a silicon carbon double bond. During these studies he developed short total syntheses of (±)-prelactone B and (±)-epipicropodophyllotoxin. Currently he is writing his Ph. D. Thesis and working as an industrial research scientist for Sanofi-Aventis in Alnwick, UK.

Dr. Patrick Steel studied chemistry at the University of Oxford where he obtained first his B. A. and subsequently, in 1988, his Ph. D., working with Prof. Jim Thomas on the total synthesis of members of the milbemycin family of natural products. Following a period as a NATO-SERC post-doctoral fellow in the group of Prof. Gilbert Stork at Columbia University, NY, he returned to the UK to a lectureship at the University of Durham. In 1996 he received a Glaxo-Wellcome Award for Innovative Organic Chemistry and in 2000/01 held a Royal Society Industrial Fellowship working at the GlaxoSmithKline research centre in Stevenage. He is currently a Senior Lecturer in Chemistry where his research interests include new organosilicon chemistry, the development of novel synthetic methodology for both classical and solid phase synthesis and projects at the chemistry/biology interface.

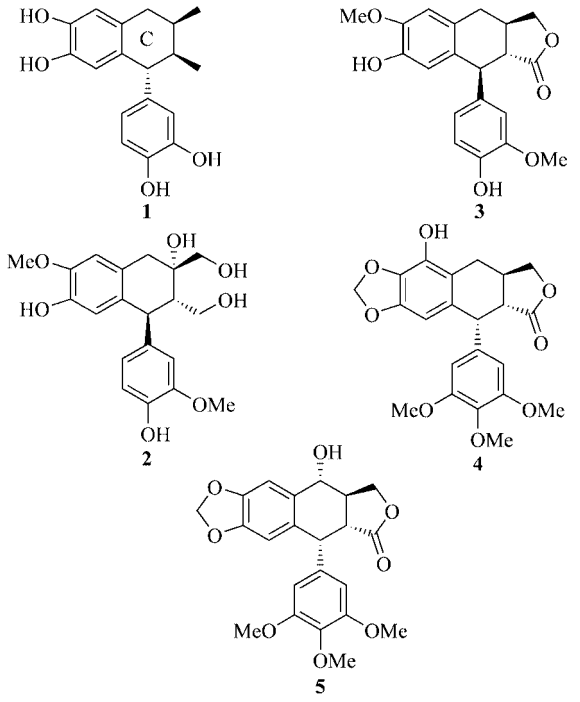


Figure 2. Typical examples of tetralin lignans.

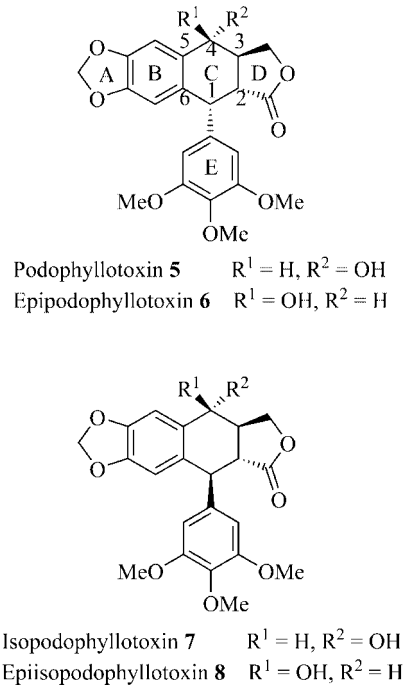


Figure 3. Podophyllotoxin and *trans*-fused stereoisomers.

C ring. This lactone fusion may have either *cis* or *trans* stereochemistry. Further functionalisation of the C ring occurs at C4.

The most prominent member of this group of natural products is podophyllotoxin (**5**). This compound, together with analogues **6**–**8** are aryltetralin lignan lactones isolated from the American Mayapple (*Podophyllum peltatum*) and related Indian species (*Podophyllum emodi*). Podophyllotoxin (**5**) has long been known to possess anti-mitotic activity with early clinical trials showing it to be highly efficacious but also quite toxic (Figure 3).[5–7]

Driven by the desire to enhance this biological profile, there have been many synthetic modifications to the podophyllotoxin structure including the generation of the three potent anticancer agents **9**, **10** and **11** (Figure 4).[8] Etoposide (**9**) and tenoposide (**10**) are DNA topoisomerase II inhibitors presently in clinical use for the treatment of many cancers, particularly small cell lung carcinoma and testicular cancer. However, neither is optimal, for example, etoposide and its analogues suffer from poor solubility and growing drug resistance. Consequently, further analogues continue to be described.[9] One such analogue is GL-331 (**11**), which is currently undergoing phase II clinical trials. GL-331 has been shown to be more potent than etoposide as a topoisomerase II inhibitor and, more notably, has overcome multidrug resistance in cancer cells, including etoposide-resistant cancer cells.[10]

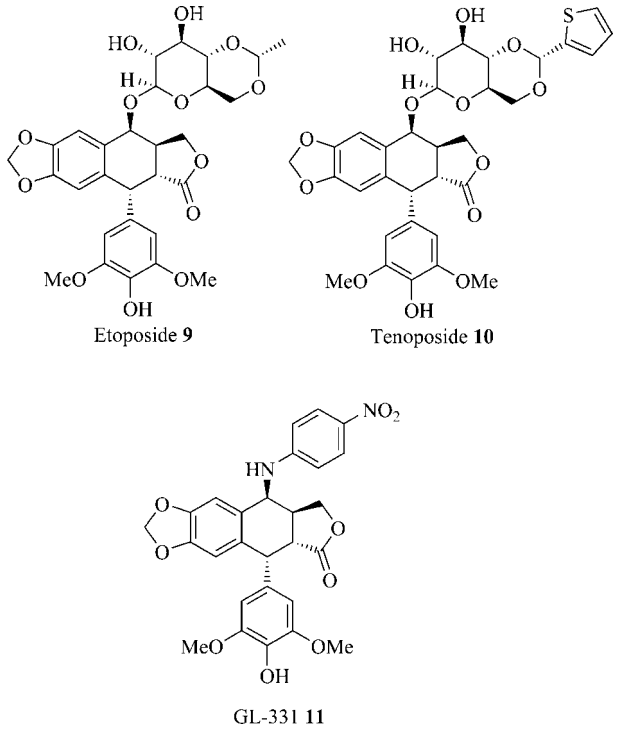


Figure 4. Synthetic analogues of podophyllotoxin.

In vivo studies have shown that metabolic deactivation of etoposide occurs through two key pathways (Figure 5).[11–13] Epimerisation of the *trans* lactone to the *cis* isomer **12** leads to a 100-fold loss in activity. Alternatively, hydrolysis of the lactone with concomitant epimerisation leads to the hydroxy acid **13**, which is 500-fold less active than etoposide. It can be deduced from these two observations that the stereochemistry surrounding the C ring of podophyllotoxin (**5**) is critical for the overall activity of the molecule. Reflecting this potent activity and stereochemical complexity the aryltetralin lignan lactones have attracted considerable synthetic interest from research groups around the world. Moreover, the fact that aryltetralin lignan lac-

tones, such as podophyllotoxin, are still isolated from natural sources in higher yields than is achieved through synthesis, renders them an even more tantalising target for the synthetic chemist.

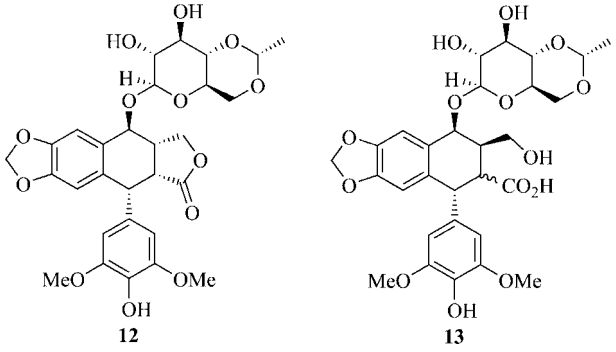


Figure 5.Metabolites derived from etoposide.

Since its first isolation in 1953 by Hartwell et al.,[14] podophyllotoxin (**5**) and its isomers have been the subject of numerous synthetic endeavours.[15–18] This microreview will briefly re-examine this earlier work and then highlight recent synthetic developments towards this goal. In particular this survey will focus on the methods, and associated stereochemical outcomes, employed in the formation of the CD ring moiety. These are organised according to the strategy used to generate and functionalise the C ring.

2. Synthetic Routes and Key Strategic Issues

Synthetic approaches towards the aryltetralin lactone skeleton follow either a linear AB → ABC → ABCD or a convergent AB + D → ABCD strategy. In both approaches the cyclisation precursor can be either assembled with all the C-ring substituents in place or these can be introduced following completion of the skeleton. In all cases, stereochemical issues dominate. The particular challenge for podophyllotoxin is in establishing the 1,2-*cis* stereochemistry together with a *trans* lactone ring fusion. This particular stereochemical combination enforces severe conformational restraints and, on mild base treatment, podophyllotoxin undergoes rapid epimerisation to afford a 97.5:2.5 mixture of picropodophyllin and podophyllotoxin.[19] Consequently, a second strategic issue is at what stage the stereochemistry at C1, C2 and C3 is finally established.

2.1 C-Ring Formation by Aryl Substitution

The most common approach to complete the aryltetralin lactone skeleton has been by electrophilic aromatic substitution forming the C1–C6 bond and simultaneously establishing the stereochemistry at C1. As indicated above this can be undertaken using acyclic precursors or with the D ring established. The latter is the most attractive and considerable effort has been expended towards this end using a three-component coupling procedure involving an acyl anion equivalent, a butenolide Michael acceptor and an aldehyde (Figure 6).

Whilst such an approach leads to the establishment of the *trans* lactone stereochemistry at an early stage, forming the 1,6 bond in this fashion has a major limitation in the preferential production of the 1,2-*trans* stereochemistry. This selectivity can be affected by the presence of additional stereochemical elements in the cyclisation process. This is highlighted by the early efforts of Zeigler, Gonzalez, Pelter and Ward who demonstrated that the precise nature of the substitution at C4 and the cyclisation conditions seem to be crucial (Scheme 1). For example, $SnCl_4$-promoted cyclisation of aryl carbinol **14** and subsequent dithiane deprotection afforded a single product **15** with the 1,2-*trans* rather than the desired 1,2-*cis* configuration (Scheme 1, a).[20] Similarly, when the C4 dithiane substituent was reductively cleaved prior to cyclisation with TFA, the aryl lignan lactone **17** was generated with isopodophyllotoxin stereochemistry (Scheme 1, b).[15,21–23] In contrast to these observations, TFA-mediated cyclisation and dithiane hydrolysis of the 4-hydroxyphenyl-containing carbinol **18** afforded a mixture of the podophyllotoxin and picropodophyllin isomers **19** and **20** (Scheme 1, c).[24] This unusual contrathermodynamic isomerisation has been reinvestigated and it appears that control of the stereochemistry through manipulation of the aryl substituents is unlikely to provide efficient access to the podophyllotoxin series.[25] A highly *cis*-selective cyclisation is observed in the related cyclisation of arylcarbinol **21** which can be attributed to the additional constraints enforced by the fused silacyclic acetal (Scheme 1, d).[26]

In the drive for enhanced synthetic efficiency, this highly convergent approach continues to attract significant attention. More recent attempts have explored cyanohydrins and sulfoxides as the acyl anion equivalent.[27–30] Whilst the former are efficient, careful control of pH in the regeneration of the ketone function is necessary to avoid epimerisation at C3. Application of sulfoxide anions seems to avoid this problem and Bhat has used a chiral sulfoxide in an exceptionally concise asymmetric synthesis of podophyllotoxin (Scheme 2, a).[31] This synthesis is particularly noteworthy as TFA-mediated cyclisation of aryl carbinol **25** followed by sulfoxide hydrolysis afforded podophyllotoxin albeit in low yield. The formation of the desired 1,2-*cis* stereochemi-

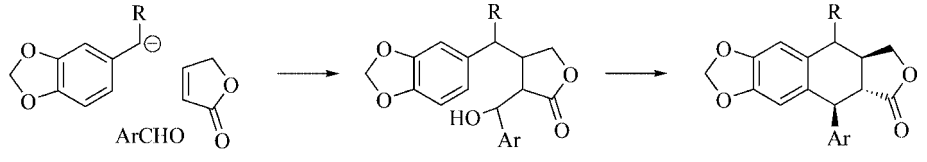
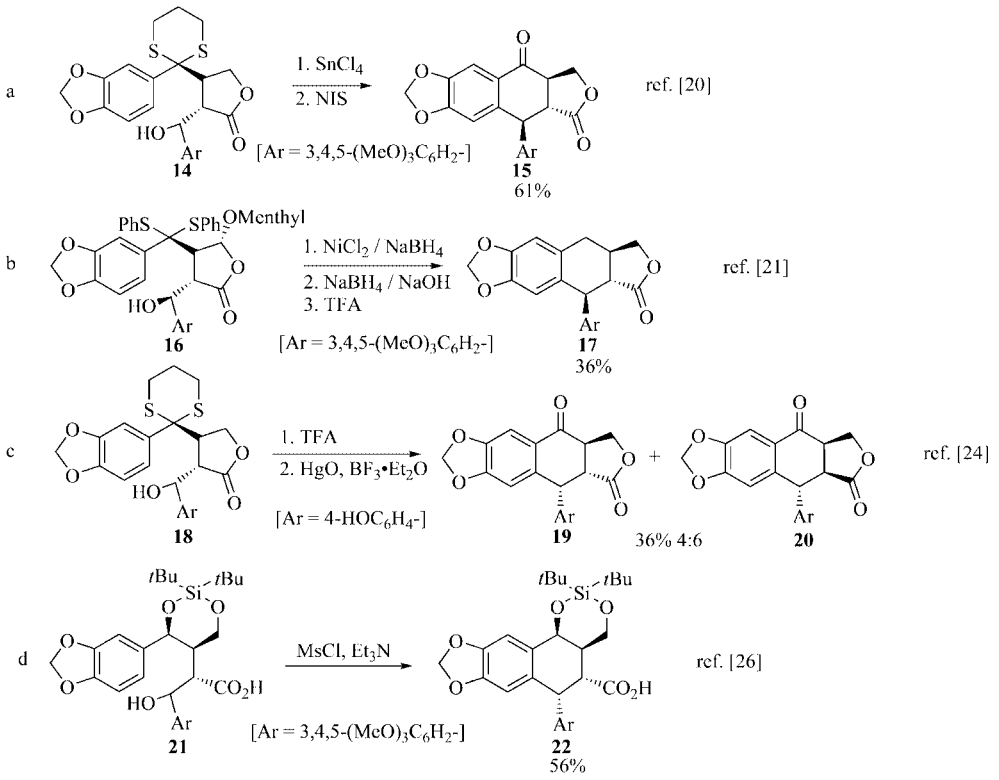


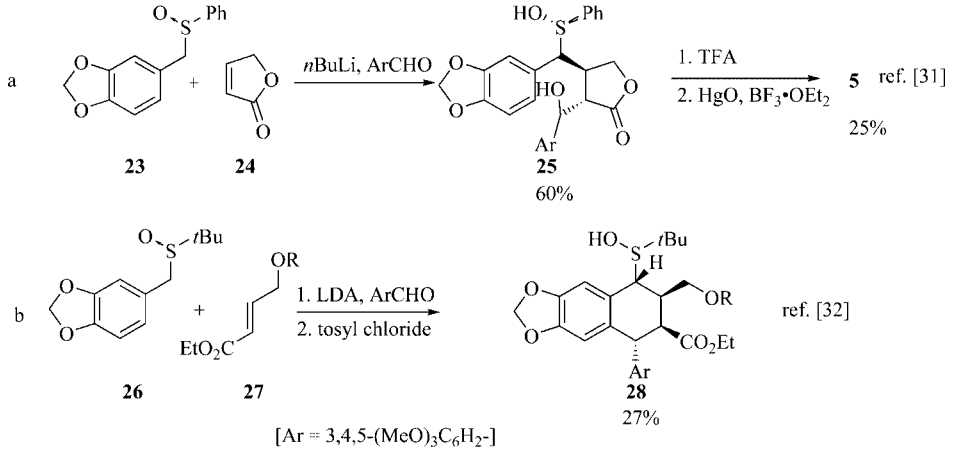
Figure 6. Three-component coupling strategy for aryltetralin lignan lactone synthesis.



Scheme 1.

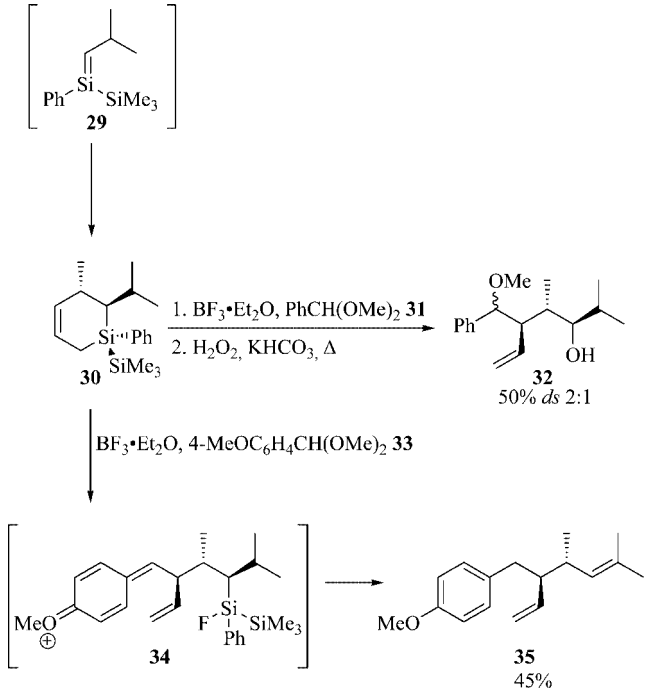
cal arrangement in such an acid-catalysed cyclisation is unusual. Casey has subsequently demonstrated that the isolation of the aryl carbinol can be avoided (Scheme 2, b).[32] Following tandem conjugate addition–aldol condensation between sulfoxide **26**, crotonate **27** and 3,4,5-trimethoxybenzaldehyde, in situ tosylation afforded the tetralin skeleton in a single operation. However, in this case the normal 1,2-*trans* stereochemistry was produced. Subsequent C–S to C–O conversion and lactonisation of the D ring afforded picropodophyllotoxin. In further contrast to the report by Bhat, attempts to enhance the synthetic efficiency through the use of an intact D ring (butenolide) in the conjugate addition were not successful.

Our approach to the synthesis of the aryltetralin skeleton similarly assembles the complete C ring in a single operation. As part of a project exploring the use of silenes, compounds containing a Si=C double bond, for example, **29**, as novel reagents for organic synthesis we have prepared silacyclohex-4-enes through a silene-diene [4+2] cycloaddition reaction.[33–35] We established that these cyclic allylsilanes undergo a Lewis acid promoted Sakurai-type reaction with aryl and alkyl acetals to give monoprotected 1,4-diols, for example, **32** (Scheme 3).[36] However, when electron-rich aromatic acetals are employed the initial adduct is a vinylogous acetal which can react further to provide a second oxonium ion (*p*-quinone methide **34**). For example,



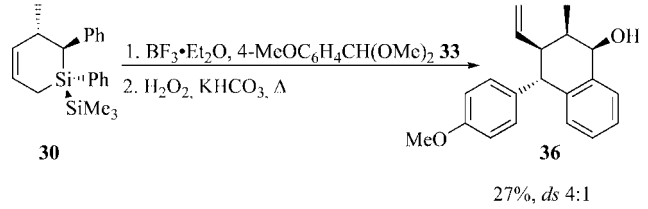
Scheme 2. Tetralin synthesis via tandem conjugate addition–aldol reactions of sulfoxide anions.

$BF_3{\cdot}Et_2O$-promoted reaction of silacyclohex-4-ene **30** with acetal **33** afforded the non-conjugated diene **35** via intramolecular hydride transfer to the *p*-quinone methide **34** to afford a β-silicon-stabilised carbocation and subsequent loss of the silyl group.



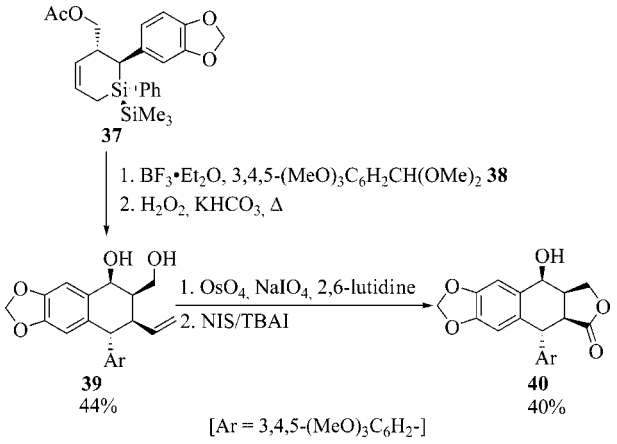
Scheme 3.

In a related fashion, 2-arylsilacyclohex-4-enes, for example, **30**, form a similar cationic intermediate which is trapped through a silicon-directed electrophilic aromatic cyclisation reaction (Scheme 4). Subsequent Fleming–Tamao oxidation of the resultant silyl fluoride leads to the tetrahydronaphthalene **36** in good yield.[37]



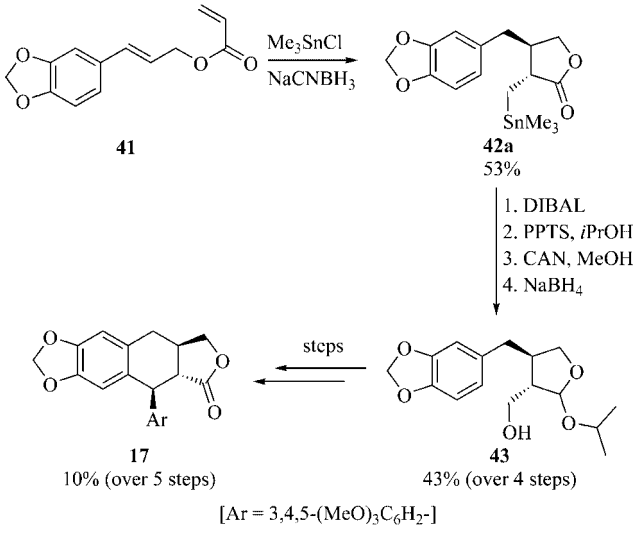
Scheme 4.

Application of this method to the synthesis of the aryltetralin lignan lactones proceeded smoothly. Combination of piperonal-derived silacyclohexene **37** with acetal **38** afforded, following Fleming–Tamao oxidation, tetrahydronaphthalene **39** in 44% yield as a single diastereoisomer. The *trans,cis,cis* stereochemistry surrounding the C ring was confirmed by NOESY NMR experiments. The D ring lactone was then installed by a two-step sequence to produce epipicropodophyllin (**40**) in good yield (Scheme 5).[38]



Scheme 5.

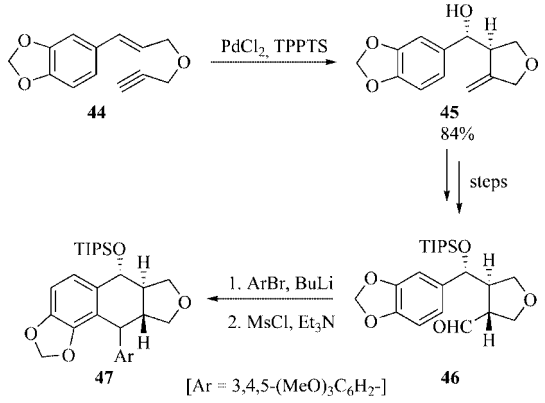
Whilst these highly condensed sequences are attractive, considerable effort has also been applied to more stepwise approaches involving the initial preparation of a D ring unit establishing the 2,3-*trans* stereochemistry at an early stage. For example, $Me_3Sn^{\cdot}$-initiated carbocyclisation of diene **41** afforded a 4:1 *trans*/*cis* mixture of lactones **42a** and **42b** (not shown).[39,40] Protection of the lactone carbonyl group as an acetal, oxidative cleavage of the C–Sn bond with CAN in MeOH, followed by reduction with $NaBH_4$ then afforded a separable mixture of acetal isomers **43**. Following elaboration to the aryl carbinol, acid-catalysed cyclisation was explored in the hope that the acetal stereocentre would influence the stereochemistry. However, this proved not to be the case with cyclisation affording deoxyisopodophyllotoxin (**17**) in moderate yield accompanied by various polycyclic byproducts (Scheme 6).



Scheme 6.

Genet has described a method for the production of a D-ring aldehyde **46** by a novel carbohydroxypalladation cycloisomerisation of a 1,6-enyne (Scheme 7). Importantly the reaction also installs the desired hydroxy function at C4 with exclusive 3,4-*trans* selectivity.[41] Whilst this could be

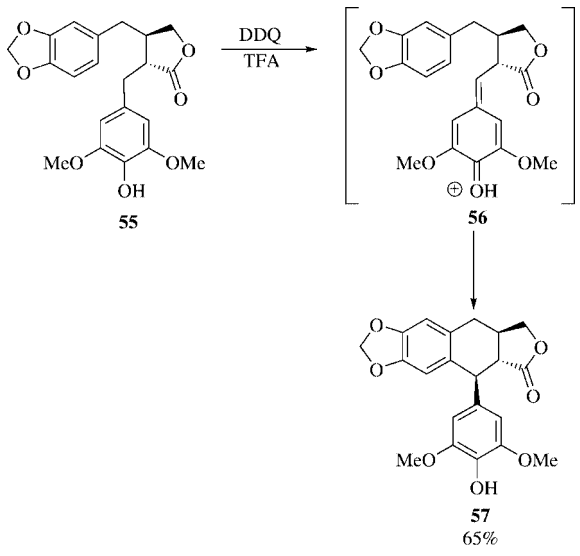
elaborated to a cyclisation precursor containing the correct podophyllotoxin stereochemistry at C2, C3 and C4, treatment with MsCl and Et_3N afforded the alternative tetracycle **47**. The reasons for this are not immediately obvious, as many similar examples provide the desired cyclisation products (cf. Scheme 1).



Scheme 7.

One challenge in many of these methods lies in establishing the absolute stereochemistry. Reflecting the control obtained in electrophilic additions to enolates derived from β-substituted butyrolactones, a popular approach has been to develop enantioselective syntheses of this versatile intermediate and then elaborate this to the aryltetralin lactone skeleton. The initial asymmetric centre has been established in a number of ways including by asymmetric hydrogenation of succinates[42] (Scheme 8, a), C–H insertion of diazo esters,[43] (Scheme 8, b) and enolate alkylation[44] (Scheme 8, c). In this context it is pertinent to note that Pelter has demonstrated that the three-component coupling reaction of enantiomerically pure 5-menthyloxyfuranone proceeded with complete diastereoselectivity (see Scheme 1, b).

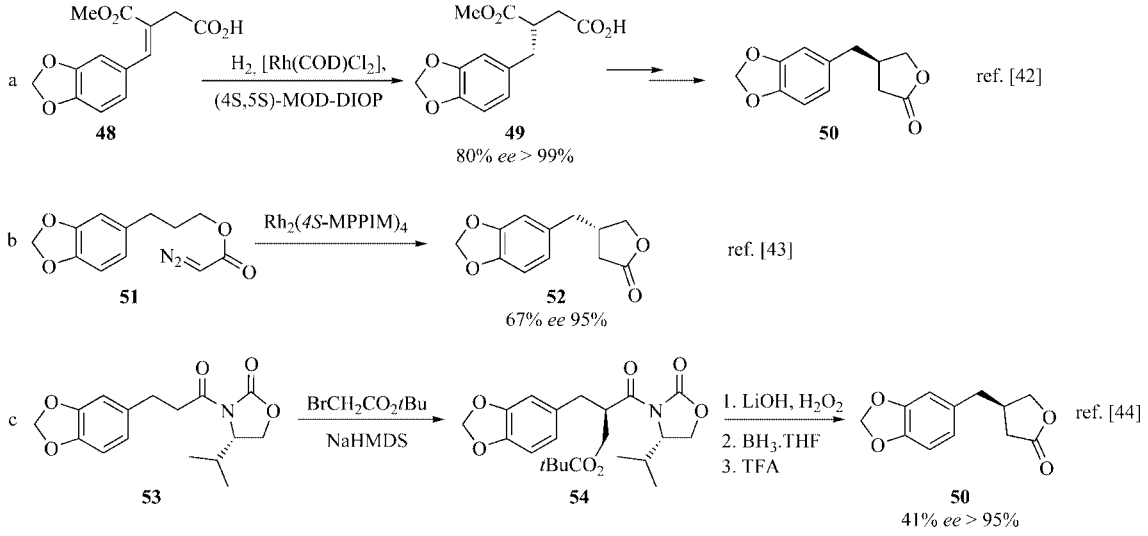
Whilst the majority of syntheses involving C-ring formation by aromatic substitution follow an S_EAr pathway using a stabilised cation derived from a C1 aryl carbinol, other strategies have been explored. Similar cationic intermediates (quinone methides) are probably generated in the oxidation of 4′-demethylyatein (**55**) with DDQ in the presence of TFA which also affords the isopodophyllotoxin stereochemistry (Scheme 9).[44]



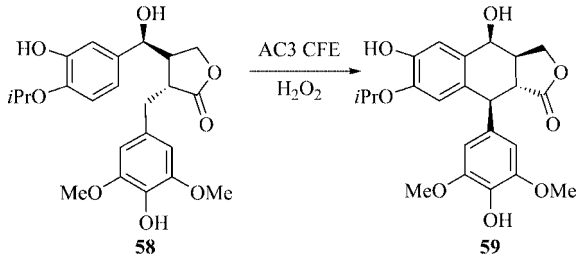
Scheme 9.

This benzylic oxidation is suggested to be a biomimetic process.[45] In support of this Kutney and others have shown that various oxidative enzymes can promote a similar transformation.[46,47] For example, treatment of the butanolide **58** with a cell-free enzyme preparation derived from *Catharanthus roseus* (AC3 CFE) led directly to a fully substituted C-ring lactone possessing *cis*,*trans*,*trans* stereochemistry (Scheme 10).

Alternatively, the corresponding C1 ketone **60** can be used as the cyclisation substrate. This, on acid treatment leads to the unsaturated lactone derivative **61**. Saponifica-

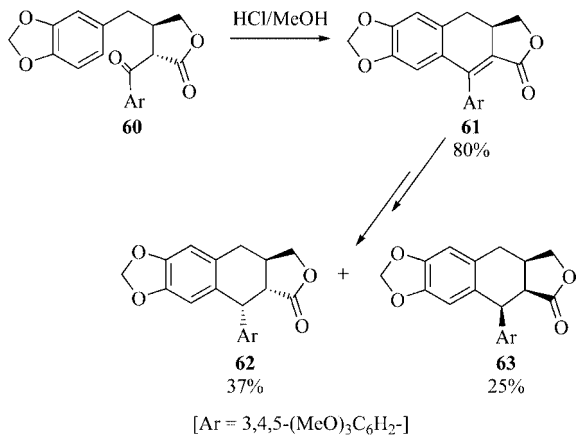


Scheme 8. Selected examples of asymmetric lignan syntheses.



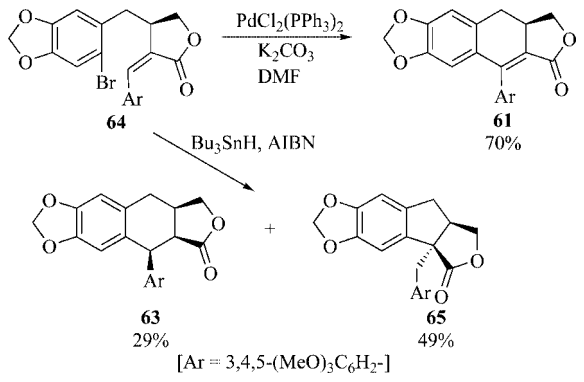
Scheme 10.

tion of the D ring followed by reduction and recyclisation afforded the desired 1,2-*cis* stereochemistry, albeit as a mixture of lactone stereoisomers **62** and **63** (Scheme 11).[42]



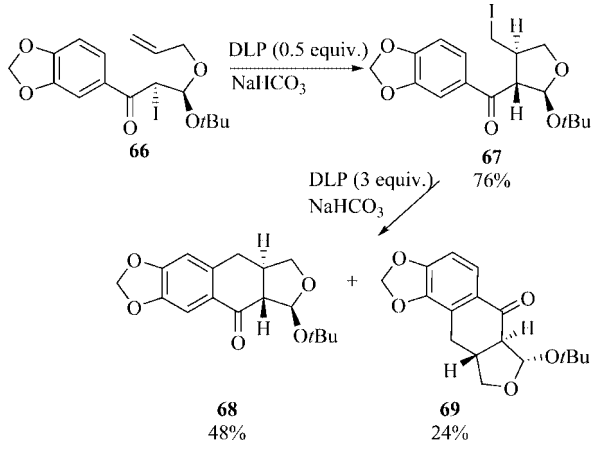
Scheme 11.

A similar unsaturated lactone is generated in a novel Heck cyclisation developed by Ishibashi and Ikeda (Scheme 12).[48] In this approach the stereochemistry of the starting alkene is crucial. Whilst use of the (*Z*) lactone **64** affords a good yield of apopicropodophyllin (**61**), similar treatment of the (*E*) isomer results in a complex mixture of products. This is suggested to result from the latter isomer requiring a pseudo-axial aryl group in the transition state inhibiting the desired cyclisation. Attempts to achieve this ring closure using radical means were less successful with both isomers favouring the 5-*exo* pathway, the (*E*) lactone doing so exclusively.



Scheme 12.

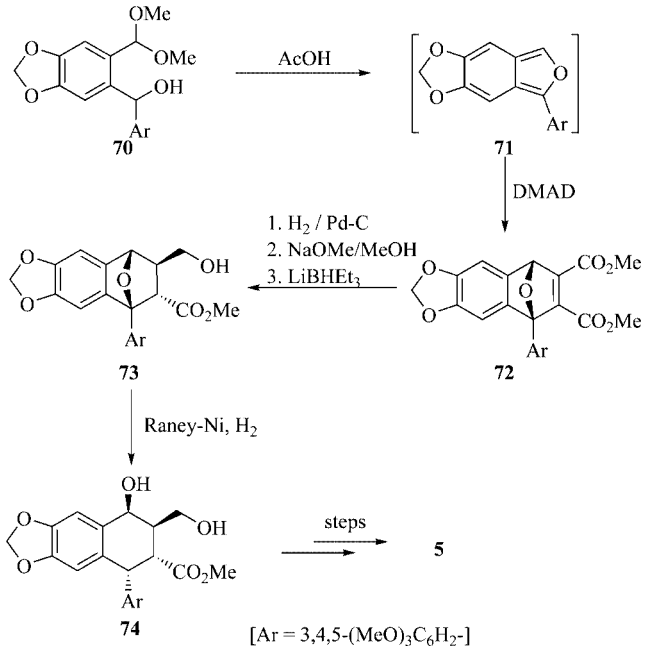
Finally, a conceptually different free-radical-mediated approach to the podophyllotoxin skeleton, involving formation of the C4–C5 bond in a cascade cyclisation sequence, was reported by Renaud (Scheme 13).[49] Treatment of iodide **66**, synthesised in four steps from piperonoyl chloride, with 0.5 equivalents of dilauroyl peroxide (DLP) afforded the D-ring acetal **67** as a single isomer. Subsequent reaction with excess DLP generated the ABCD ring system albeit accompanied by significant quantities of the regioisomeric tetracycle **69**. Attempts to undertake the cascade in a single process also produced **68** in a similar overall yield but only as a component of a complex mixture of products that was difficult to separate.



Scheme 13.

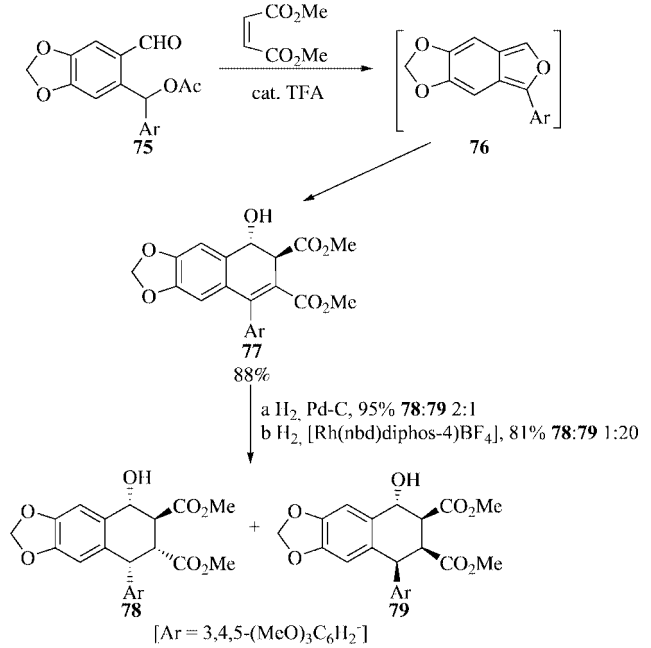
2.2 C-Ring Formation by Cycloaddition Reactions

The other principal strategy for the construction of the C ring has been the Diels–Alder reaction. This has the advantage of installing much of the stereochemistry in a single operation. The challenge of this approach is the generation of a diene component that provides efficient stereocontrol of all centres. This strategy was pioneered by the work of Rodrigo who recognised that the oxabicyclic adduct **72** derived from isobenzofuran **71** and DMAD contains all the required carbon and oxygen atoms for podophyllotoxin.[50–52] Whilst the use of DMAD necessitates the additional steps of reduction and C3 epimerisation, these proceed efficiently and are preferable to a more direct fumarate cycloaddition as the latter leads to a mixture of *endo*/*exo* stereoisomers (vide infra). Importantly, the reductive cleavage of the oxa bridge with Raney nickel occurs chemo- and stereospecifically, with retention of the C1 stereochemistry, establishing the 1,2-*cis*-2,3-*trans* relationship. When combined with the efficient lactonisation procedure developed by Jones,[53] this provides rapid access to epipodophyllotoxin (**6**) and, after C4 epimerisation, podophyllotoxin (**5**) in 19 and 11% yields from piperonal, respectively (Scheme 14).



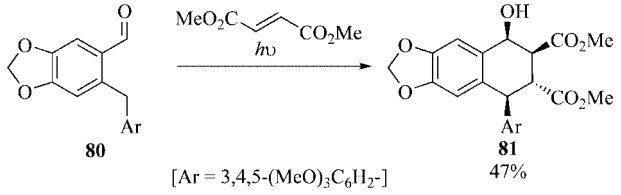
Scheme 14.

Alternatively, acid-catalysed elimination of the oxa bridge leads to the dihydronaphthol **77** and catalytic reduction of this leads to the desired 1,2-*cis* stereochemistry.[54] Whilst simple reduction of **77** with H_2, Pd/C gave a 1:2 mixture of the picropodophyllin/podophyllotoxin isomers **79** and **78** (Scheme 15), hydroxy-directed reduction using the cationic rhodium complex [Rh(nbd)(diphos-4)-BF_4] afforded enhanced selectivity, 20:1 in favour of **79**.



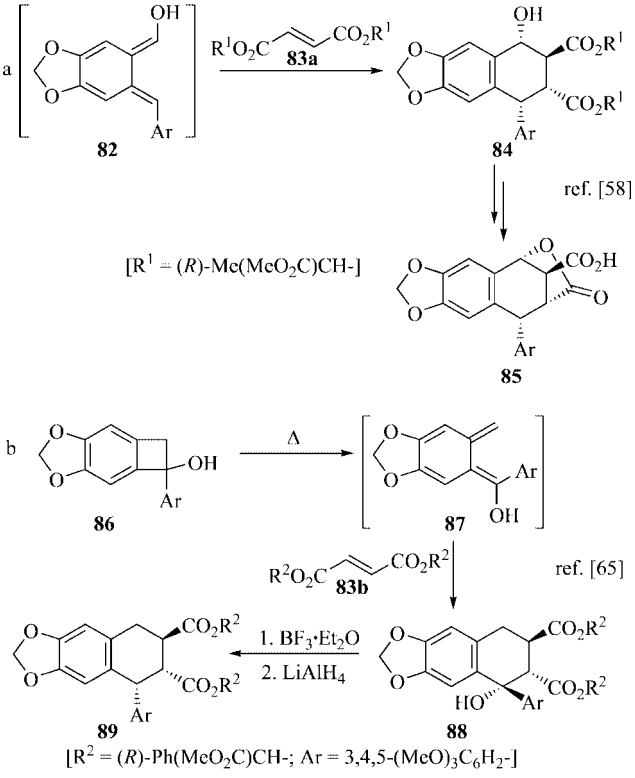
Scheme 15.

A range of other dienophiles have been employed in these reactions with *o*-quinodimethide equivalents. However, the regioselectivity observed is frequently only modest when non-symmetrical dienophiles are used.[55–60] For this reason a number of approaches have used simple symmetrical maleate systems exploiting the greater accessibility of the C3 carbonyl group for subsequent selective epimerisation and reduction of the cycloadduct.[61,62] The particular problems of fumarate cycloadditions are illustrated by the early work of Durst (Scheme 16).[63] In this, an *o*-quinodimethide is generated and trapped in a photo-enolisation Diels–Alder strategy. Whilst reaction with methyl fumarate established the *syn* C1 and C4 arrangement it also leads to the formation of the alternative epiisopodophyllotoxin *trans,trans,cis* stereochemistry.



Scheme 16.

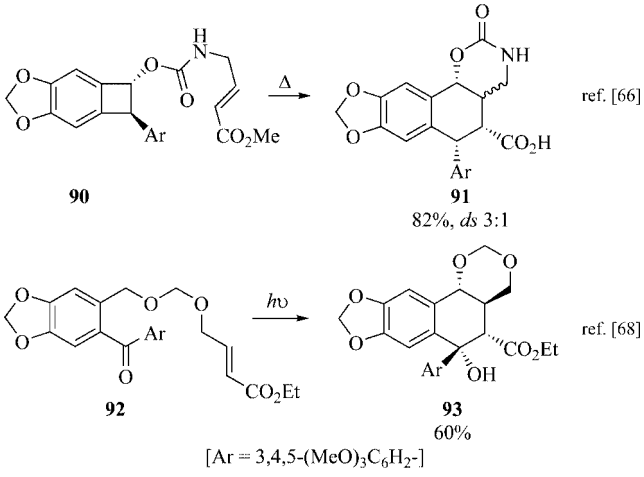
Charlton has proposed two solutions to this problem. The first was based on the observation that the fumarates of lactate and mandelate **83** lead preferentially to an *exo* adduct.[64] The reasons for this are not immediately clear but have been exploited to provide a short synthesis of neopodophyllotoxin (**85**) (Scheme 17, a).[58] The second strategy was to use α-hydroxy-α-aryl-*o*-quinodimethide **87** in which the hydroxy group would control the regio- and stereochemistry of the cycloaddition. The *o*-quinodimethide was generated from the corresponding benzocyclobutane **86**



Scheme 17.

with the ring-opening giving the (*E*) 'diene', as predicted by torqueselectivity rules. Whilst this generated the required 2,3-*trans* stereochemistry, reduction of the C1 hydroxy group with inversion proved not to be trivial. After some experimentation a combination of $BF_3{\cdot}OEt_2$ and $LiAlH_4$ proved successful giving a 15:2 mixture of the C1 α and β isomers with the major isomer **89** being elaborated to deoxypodophyllotoxin (Scheme 17b).[65]

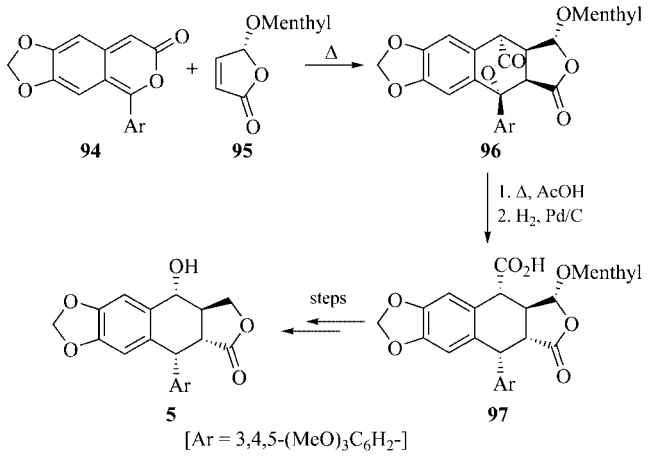
An alternative solution to the problem of controlling the selectivity of crotonate cycloadditions is to carry out the Diels–Alder reaction in an intramolecular fashion using a C4-linked tether. In this way the activating group on the dienophile is forced to occupy the C2 position and then an *endo* transition state leads to the desired podophyllotoxin stereochemistry (Scheme 18).[66–68]



Scheme 18.

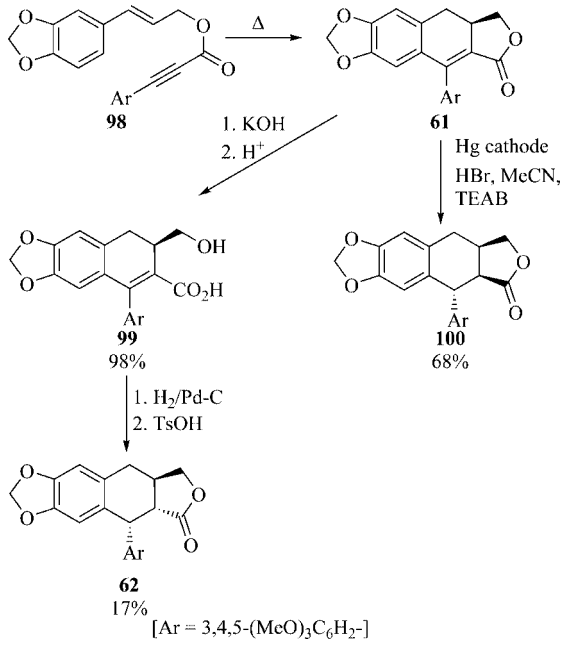
The challenge of controlling the stereo- and regiochemistry of addition to *o*-quinonedimethide-type dienes has also been studied by Jones. In an elegant series of papers, using the readily accessible and sometimes isolable pyrones **94**, it was shown that whilst a C2 aryl substituent induces an *exo* orientation for a methoxy carbonyl group at C2 this directing effect can be overcome by using more compact dienophiles.[69–71] Whilst the lactate fumarate **83a** used by Charlton proved non-selective, the menthyloxyfuranone **95** gave complete selectivity for the *endo* adduct. Following acid-promoted elimination of the lactone bridge, hydrogenation afforded the podophyllotoxin 1,2-*cis*-2,3-*trans* stereochemistry (≈7:1) with the selectivity directed by the chiral auxiliary. Subsequent C4 oxidative decarboxylation, hydrolysis of the chiral auxiliary, reduction and lactonisation afforded (–)-podophyllotoxin (**5**) in 15% overall yield from pyrone **94** (Scheme 19).[59]

Whilst the Diels–Alder reaction is most commonly undertaken to realise a 1,2 3,4 disconnection strategy, Klemm and Yamaguchi have reported an alternative 2,3 1,6 bond construction strategy involving the intramolecular Diels–Alder reaction of propargylic ester **98**. Whilst catalytic reduction of the lactone **61** afforded the all-*cis* isomer, use of the free hydroxy acid **99** led to the desired 1,2-*cis*,2,3-*trans* stereochemistry, albeit in low yield (Scheme 20).[72] As with



Scheme 19.

the Kondo approach (Scheme 15),[54] this presumably reflects a hydroxy-directed reduction. Alternatively electrochemical reduction of unsaturated lactone **61** led to the 1,2-*trans*,2,3-*cis* picropodophyllin stereochemistry.[73]

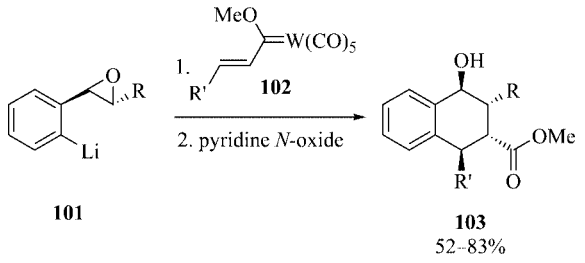


Scheme 20.

2.3 Other Modes of C-Ring Construction

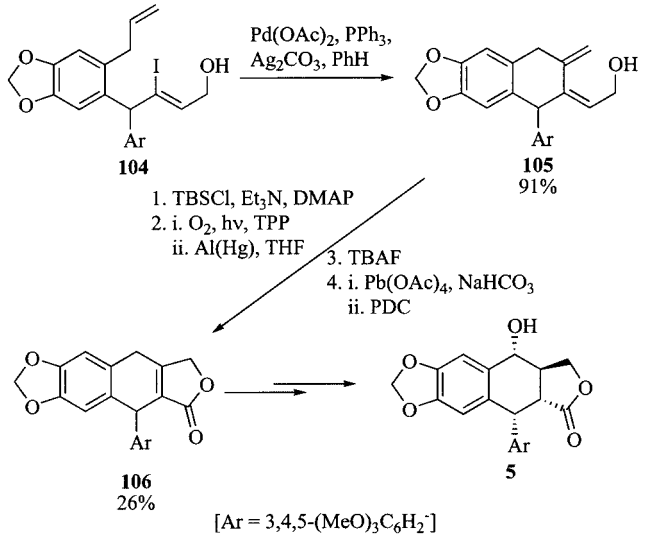
Whilst the majority of approaches to the podophyllotoxin C ring follow one of the two strategies described above, a few methods have been used to complete the ring through the formation of the 2,3 bond. In the main, this reflects the ability to generate an enolate anion at C2 due to the presence of the future lactone carbonyl group. The process can be rendered very convergent by application of a Michael-induced ring-closure (MIRC) sequence and can

be achieved in a very concise fashion (Scheme 21).[74,75] The drawback to such an approach is the formation of the undesired 1,2-*trans* stereochemistry.



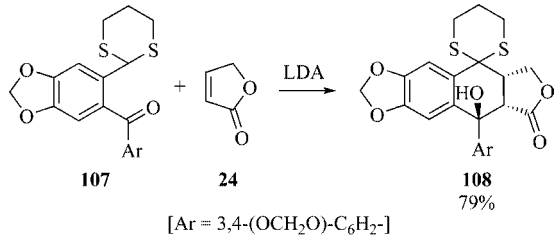
Scheme 21.

In a unique approach to the aryltetralin skeleton, Toste employed an intramolecular Heck reaction of vinyl iodide **104** to construct the C ring in his synthesis of podophyllotoxin (Scheme 22).[76]



Scheme 22.

Lastly, in a complementary approach to the tandem conjugate addition strategy described earlier, Harrowven has assembled the C ring by the construction of the 1,2 and 3,4 bonds through a type II MIRC procedure (Scheme 23).[77]

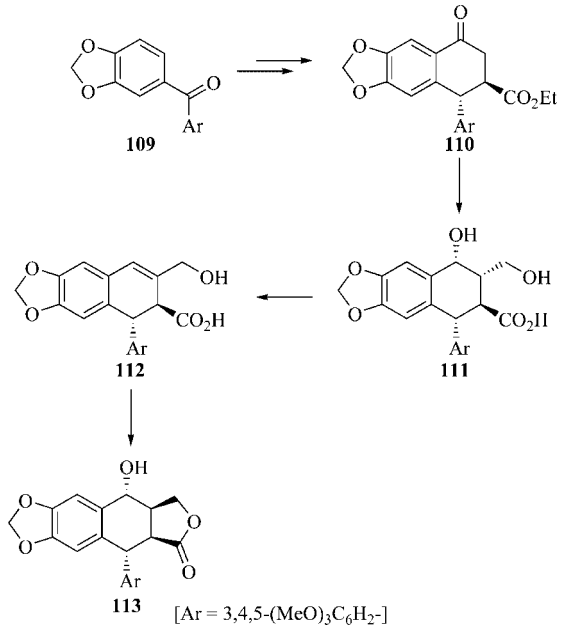


Scheme 23.

2.4 Functionalisation of the Preformed C Ring

The other principal strategy for the preparation of podophyllotoxin relies on an early construction of the C ring and then subsequent introduction of the remaining functionality and manipulation of the stereochemistry. In this respect it is pertinent to note that conditions for the interconversion of various podophyllotoxin diastereoisomers have been established, notably that of picropodophyllin.[19] Thus, synthesis of the other stereochemistries can be considered as formal syntheses of podophyllotoxin itself. Interestingly, conversion of deoxypodophyllotoxin to podophyllotoxin by microbial oxidation has been described and thus this compound can also be considered as an appropriate endpoint.[78]

In many cases the C ring is initially established using methods discussed in the previous section. The first synthesis of podophyllotoxin, reported in 1962 by Gensler, followed such an approach. In an earlier relay synthesis of picropodophyllin, Gensler had identified the tetralone **110** as a key C-ring precursor.[79,80] Oxo ester **110** was generated in four steps from benzophenone derivative **109** through a sequence involving Stobbe condensation, reduction, activation of the carboxylic acid and Friedel–Craft acylation.[81] Introduction of the hydroxymethyl side-chain was achieved by Claisen condensation with ethyl formate followed by reduction. Subsequent dehydration and lactone saponification afforded α-apopodophyllic acid **112** which could be resolved using quinine. Lactonisation and hydration of the alkene then afforded picropodophyllotoxin **113** albeit in low yield (Scheme 24).[82]

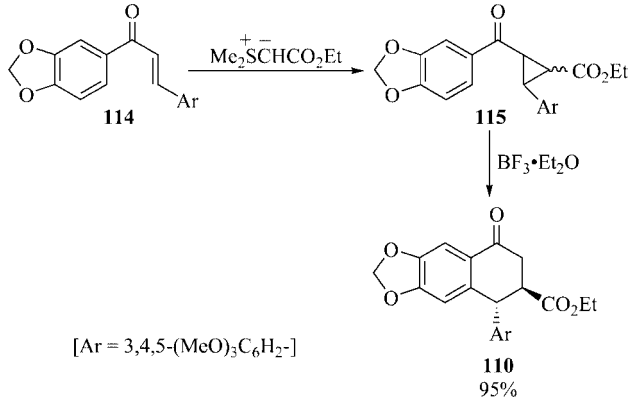


Scheme 24.

Whilst this established the basic skeleton of aryltetralin lactones, the stereochemistry represented the thermodynamically favoured outcome. However, based on earlier studies exploring the picropodophylin–podophyllotoxin equilibrium, Gensler proposed that kinetic reprotonation of the relatively planar lactone enolate would proceed from the less hindered β face to afford the desired *trans* lactone. Importantly, proceeding via picropodophyllin establishes the correct stereochemistry at C3 through the preferential

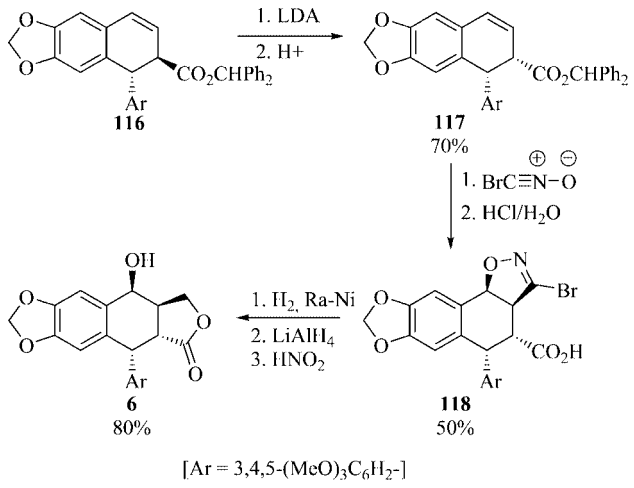
formation of a *cis* lactone. Consequently, following alcohol protection as the THP acetal, enolate formation with triphenylmethylsodium and subsequent rapid reprotonation using acetic acid, deprotection afforded a separable 45:55 mixture of podophyllotoxin and picropodohyllin.[79] The lower than expected ratio of *trans*/*cis* lactones was attributed to a high degree of pyramidalisation of the enolate in the transition state favouring the less strained picropodophyllin geometry.

Following this pioneering synthesis, others have described syntheses of podophyllotoxin via the same γ-oxo ester intermediate. However, whilst Gensler generated the C ring by a 4,5 bond connection with a 1,2-*trans* stereochemistry, most subsequent syntheses of this intermediate have completed the C ring through a 1,6 bond connection.[83–85] The most concise and efficient of these approaches to the keto ester **110** is that described by Murphy and Wattanasin[85] by Lewis acid mediated rearrangement of the cyclopropane **115** (Scheme 25).



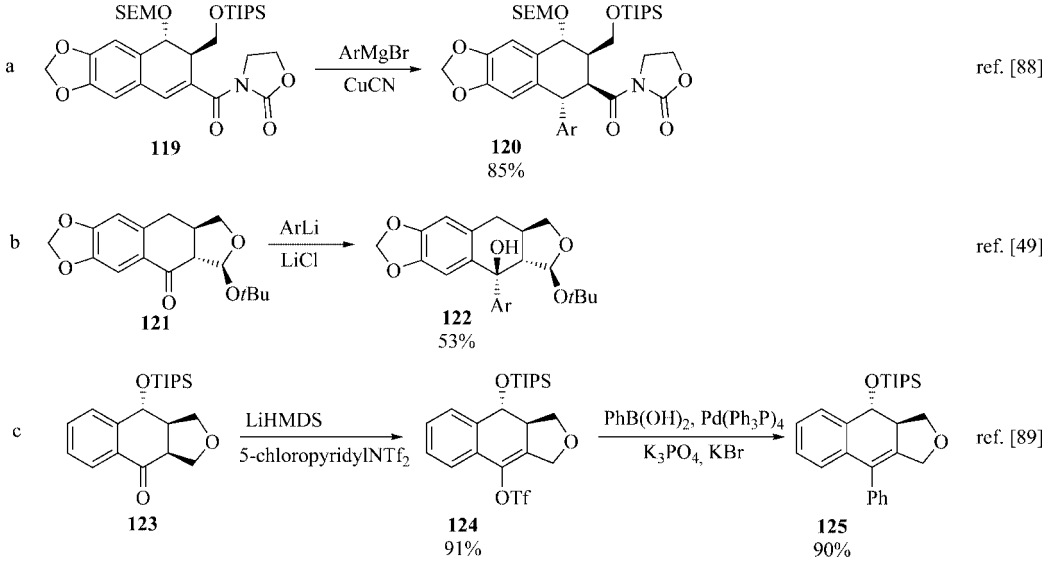
Scheme 25.

Importantly, as discussed above, in the absence of other stereocontrolling elements, all such approaches produce the 1,2-*trans* stereochemistry. Consequently, whilst the subsequent steps of the synthesis to picropodophyllone have also been enhanced, the ultimate conversion to podophyllotoxin still requires unfavourable lactone epimerisation. This challenging transformation can be addressed by carrying out the isomerisation at an earlier stage of the synthesis prior to introduction of the C3 substituent or following hydrolysis to the keto-acid.[86,87] Importantly, the former approach facilitates the stereocontrolled introduction of the C3 hydroxymethyl group as seen in the work of Vyas and Wong (Scheme 26).



Scheme 26.

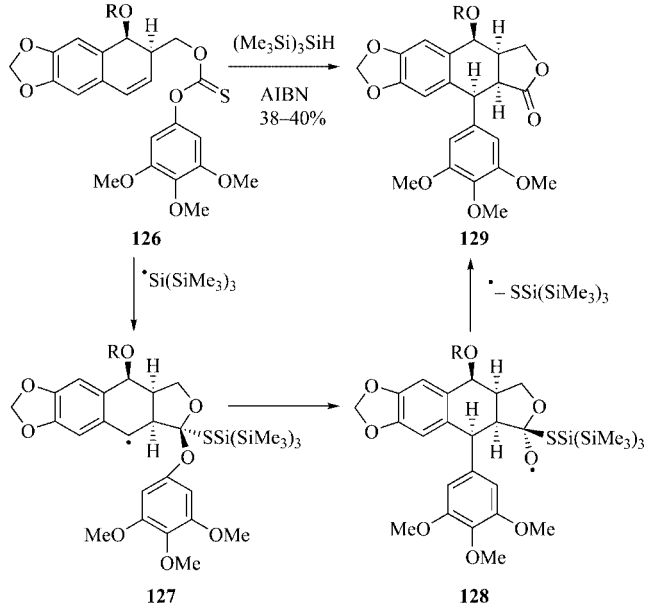
These approaches have largely established the C1 stereochemistry early in the synthesis and used this to control the introduction of the remaining stereocentres. However it is possible to reverse this process and introduce the C1 aryl group and fix the stereochemistry at this centre as part of the end game. The particular attraction for doing so is that it provides easy access to a range of analogues. Conjugate addition to the unsaturated acyloxazolidinone **119** occurs to give the desired C1 α isomer, presumably directed by the



Scheme 27.

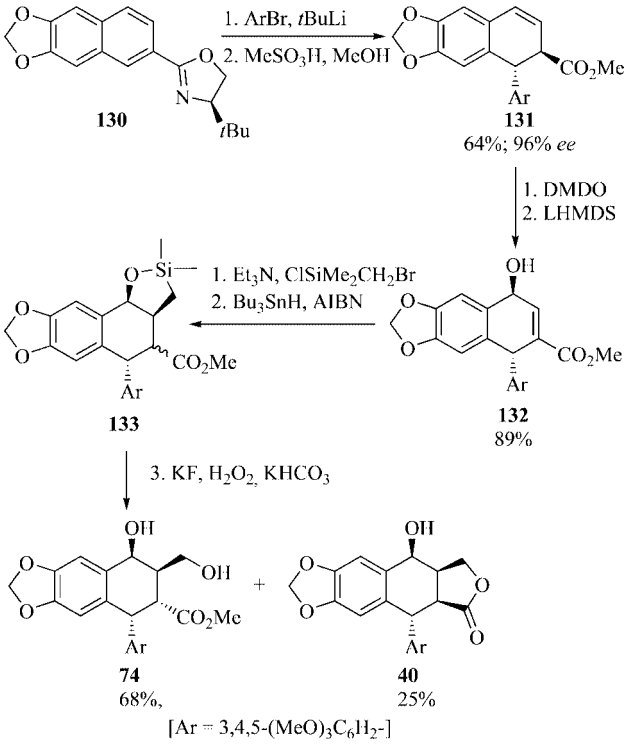
bulk of the TIPSO group at C3. Unfortunately protonation of the resultant enolate also occurs from the same face leading to the picropodophyllin stereochemistry (Scheme 27, a).[88] In the presence of LiCl, addition of an aryllithium reagent to a C1 keto lactol **121** occurs stereoselectively to afford tetracyclic aryl carbinol **122**. However, conditions for the selective reduction of the tertiary alcohol remain to be identified (Scheme 27, b).[49] Elimination to apopodophyllotoxin is possible and related reductions in this series have previously been demonstrated to provide the desired 1,2-*cis*,2,3-*trans* stereochemistry (vide supra).[42,54,72] The $\Delta^{1,2}$ unsaturated skeleton can also be accessed from the C1 ketone through enol triflate formation and Suzuki–Miyaura cross coupling (Scheme 27c).[89]

A particularly elegant approach, which simultaneously establishes the D-ring lactone and introduces the C1 aryl group, involves a tandem radical cyclisation–radical translocation sequence (Scheme 28).[90] Reflecting the tethered nature of each step, high diastereoselectivity is obtained leading to isopicropodophyllin stereochemistry. The starting thiocarbonates can be prepared in either enantiomeric series using either an Evans' asymmetric aldol–RCM sequence or a Meyers' asymmetric nucleophilic dearomatisation of a substituted naphthalene.



Scheme 28.

Enantioselective dearomatisation of a naphthalene formed a key step in one of the early syntheses of podophyllotoxin.[91] Whilst this step proved efficient, the intrinsic diastereoselectivity of the process results in the generation of 1,2-*trans* stereochemistry which required epimerisation at a late stage. This synthesis has been refined to provide (–)-epipodophyllotoxin in 96% *ee* and 30% overall yield from piperonal.[92] In this modification the key 1,2-*cis*,2,3-*trans* stereochemistry is controlled by the C1 alcohol through a silicon-tethered radical hydroxymethylation, albeit with only moderate diastereoselectivity at C2 (Scheme 29).



Scheme 29.

3. Conclusions

Although a number of elegant syntheses of podophyllotoxin have been described the challenge of assembling this structure in an efficient and completely stereoselective fashion remains an elusive goal and a valuable test for new synthetic methodology. Moreover, the biological potential of podophyllotoxin analogues and the diminishing natural supply suggest that synthetic approaches will continue to be an area of much interest.[93]

Acknowledgments

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