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ARTICLE

Recent Strategies and Tactics for the Enantioselective Total Syntheses of Cyclolignan Natural Products

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Lignan natural products are found in many different plant species and possess numerous useful biological properties, such as anti-inflammatory, antiviral, antioxidant, antibacterial, and antitumor activities. Their utility in both traditional and conventional medicine, coupled with their structural diversity has made them popular synthetic targets over many decades. This review specifically addresses the cyclolignan subclass of the family, which possess both a C8–C8' and a C2–C7' linkage between two different phenylpropene units. A comprehensive overview of the diverse strategies employed by chemists to achieve enantioselective total syntheses of cyclolignans between 2000 and early 2021 is presented.

1. Introduction

In 1936, the family of natural products characterized by a C8–C8' linkage between two phenylpropene units was given the name lignans from the Latin word *ligna*, meaning wood, in recognition of their primary source of isolation.[1] Derived exclusively from vascular plants, lignans are among the most structurally diverse natural product families known, with several sub-families used to describe common structural motifs (Fig. 1). In 1942, Haworth initially described five such sub-families, including the 1-phenyltetralins, which are characterized by an additional C2–C7' linkage and are the focus of this review.[2] The names cyclolignan (Freudenberg and Weinges, 1961)[3] and 1-arylnaphthalene (Whiting, 1985)[4] were later proposed to replace 1-phenyltetralin, although all three names for this sub-family of lignan natural products are still used in the literature today. Herein we will use the term cyclolignan as matter of simplicity. Due to their structural diversity, cyclolignan natural products exhibit a wide array of pharmacological activities, such as antiviral, antibacterial, and antineoplastic capabilities.[5] Indigenous cultures have long appreciated these medicinal qualities to treat malaria, inflammation, and a host of other ailments.[6] Contemporary examples of cyclolignan-based therapeutics are therefore unsurprising. Initially isolated from *Podophyllum peltatum*, podophyllotoxin (**1**, Fig. 2) is currently registered on the WHO Model List of Essential Medicines for the treatment of genital warts,[7] and is a potent microtubule depolymerizer that binds to the colchicine site on the tubulin subunit.[8] Its closely related analogues etoposide (**3**) and teniposide are both topoisomerase II inhibitors and have been utilized as chemotherapeutic agents.[9, 10]

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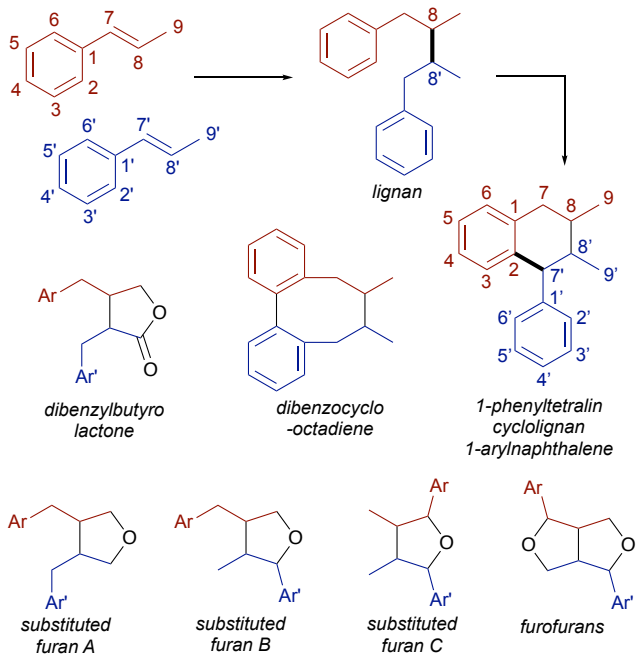

Fig. 1 Lignan natural products and lignan subgroups.

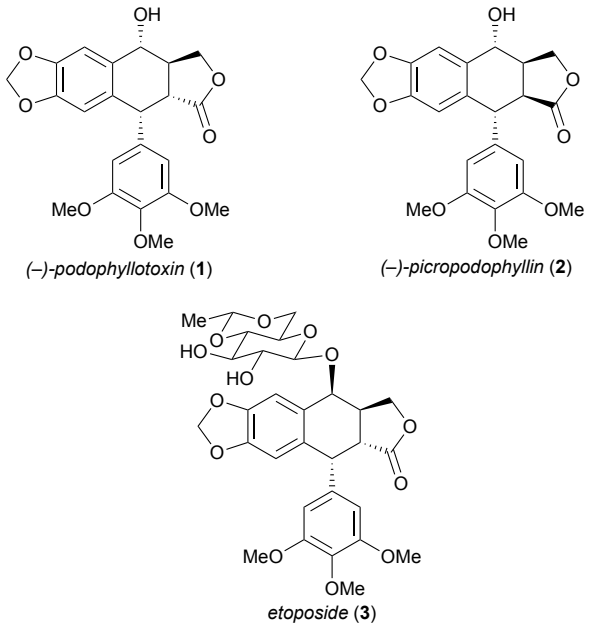

Fig. 2 Podophyllotoxin and related natural products.

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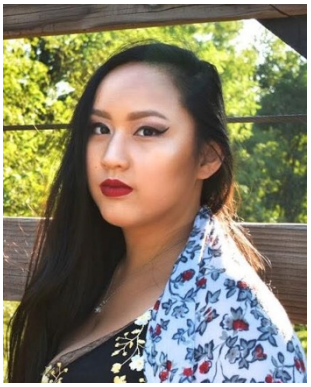

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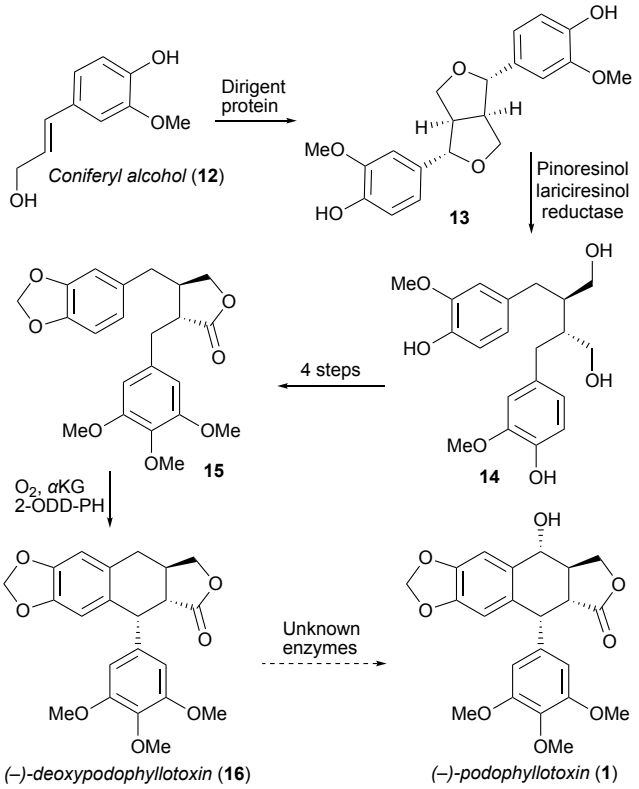
Jordan Reddel earned her B.S. in Chemistry from the University of New Hampshire in 2011, and her Ph.D. in Chemistry from Northwestern University in 2016. While working with Prof. Regan Thomson at Northwestern, she completed the total syntheses of six lignan natural products and developed an annulation methodology for the synthesis of indanes and tetralins. Dr. Reddel is currently an Associate Research Scientist and an R&D Leader of the Next Generation Synthesis group at the Dow Chemical Company.

Regan J. Thomson was born in New Zealand in 1976 and received his Ph.D. in 2003 at The Australian National University working with Prof. Lewis N. Mander. Following postdoctoral studies with Prof. David A. Evans at Harvard University, he joined the faculty at Northwestern University in 2006 where he is currently a Professor of Chemistry. Regan's research interests include reaction development, total synthesis, natural product discovery and biosynthesis, and atmospheric chemistry. He is the recipient of an NSF CAREER Award (2009), an Amgen Young Investigator Award (2010), an Illinois Division American Cancer Society Research Scholar Award (2012), and a Novartis Chemistry Lectureship (2015—2016).

2. Isolation and Biosynthesis of Lignans

Lignan natural products originate in a range of different organisms and are originally derived from the shikimic acid biosynthetic pathway.[11] Scheme 1 details the biogenesis of coniferyl alcohol (**12**), the precursor to many well-known lignan natural products.[11] Early studies into the biosynthesis of lignans focused on the oxidative coupling of phenyl propene derivatives, but even enzymatic studies led to racemic mixtures of products.[12] In 1997, Lewis isolated a protein that had no detectable catalytic active site, but instead served only to bind and orientate coniferyl alcohol-derived free radicals, which could then undergo a stereoselective coupling.[13] When this protein, named the dirigent protein, was present in solution, the furofuran lignan (+)-pinoresinol (**13**) was produced with enhanced selectivity. Recently, Fuchs and Renata developed chemoenzymatic strategies for the synthesis of (–)-podophyllotoxin (**1**) in an attempt to simultaneously improve the step-economy and remove the nonstrategic bond-forming steps of the original biosynthetic pathway (from coniferyl alcohol in Podophyllum hexandrum, Scheme 2), thus facilitating the production of **1**.[8, 14]



Scheme 2 Biosynthetic pathway for (–)-podophyllotoxin from coniferyl alcohol.

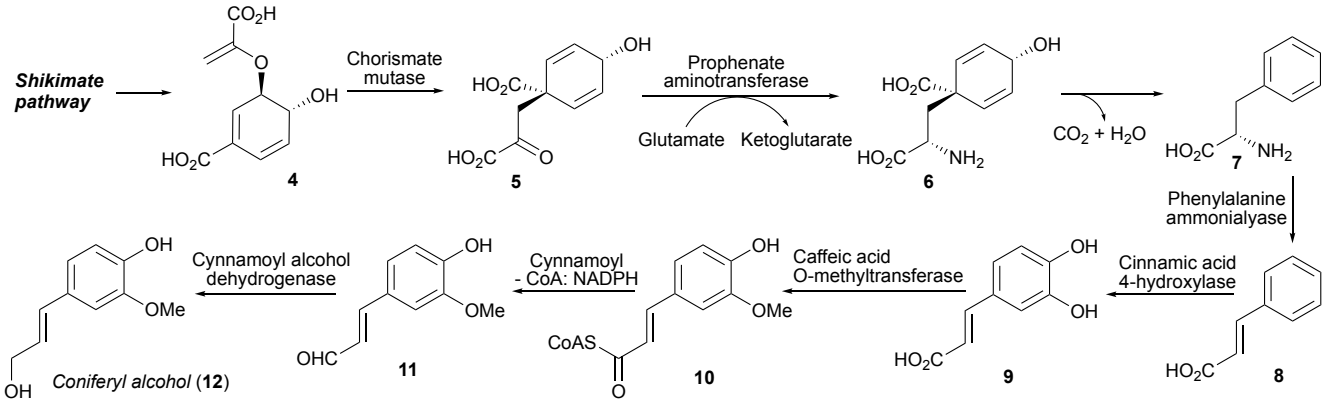
3. Enantioselective Total Syntheses of Cyclolignan Natural Products

Due to widespread interest in these lignan natural products, we cannot cover all of the synthetic efforts toward cyclolignan natural products in this report. Numerous excellent reviews have been published on the isolation and synthesis of lignan natural products including those by Whiting,[4, 15,16] Ward,[12, 17-20] and Pan,[21] and more recently Spiteller[11] and Hu.[22] This review focuses on the enantioselective syntheses of cyclolignans between the years 2000 and early 2021, with a particular emphasis on the unique strategies utilized.

3.1 Overview of Strategies used in Syntheses since 2000

Despite being relatively simple structures, the carbocyclic skeleton of cycloligan natural products lends itself to a variety of strategic disconnections that have enabled a diverse range of successful enantioselective total syntheses. Shown graphically in Fig. 3 are the four general disconnections that have formed the cornerstone of the total syntheses covered in this review (Fig. 3A), as well as one unique case (Fig. 3B).[23]

Disconnection of bond **A** (i.e., the C1–C7 bond using lignan numbering, see Figure 1) within the generic cyclolignan structure **S** leads back to a late-stage benzhydryl precursor (i.e., **a**) that has formed the foundation of the total syntheses of nine different natural products reported herein. Disconnection of the adjacent bond **B** (C7–C8) affords an isomeric benzhydryl synthon (i.e., **b**), but this approach has proven much less common, with an enantioselective synthesis of only one natural product (i.e., **1**) to date. Each of these two general approaches rely on reactions enabling the stereoselective synthesis of benzhydryl intermediates, and in this regard have been



Scheme 1 The biosynthesis of coniferyl alcohol. Adapted from the Spiteller review.

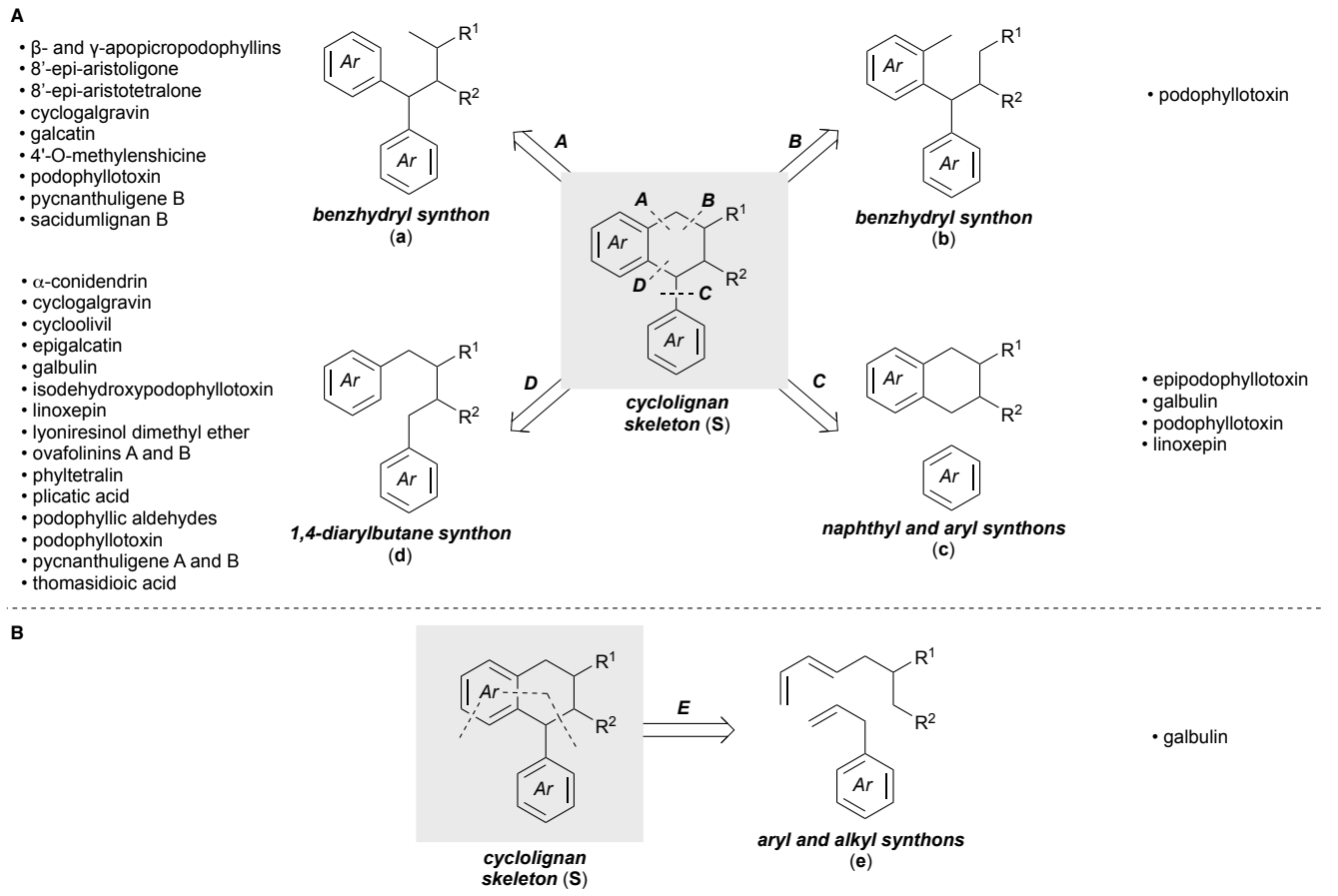


Fig. 3 Key retrosynthetic disconnections utilized for the enantioselective syntheses of cyclolignans during the period from 2000 to 2020

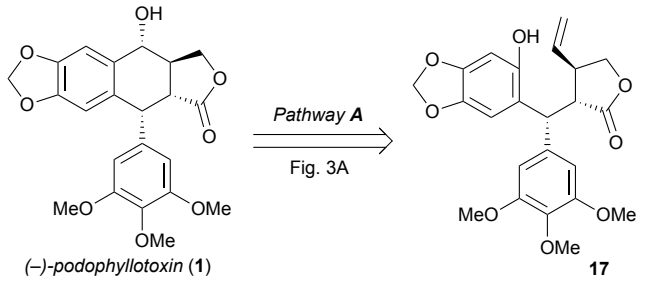
inspirational for the development of such methodology. Late-stage disconnection of bond **C** (i.e., C1'–C7') allows for the convergent assembly of the cyclolignan structure from a naphthyl synthon and the corresponding aryl fragment (i.e., **c**), and has found application in the synthesis of four different products. The most common disconnection within **S** is that of bond **D** (i.e., C2–C7'), which leads back to the 1,4-diarylbutane synthon **d** and can be considered in many cases to represent biomimetic or biosynthetically-inspired strategies. Fifteen different enantioselective cyclolignan natural products have been prepared using this key disconnection, with major challenges associated with controlling the stereochemical relationship between the C8 and C8' substituents. Figure 3B shows the unique disconnection of the aromatic ring and between the C7'–C8' bond to form aryl and alkyl synthons **e**, used by Hong and coworkers in the synthesis of galbulin via a tandem double conjugate addition-aldol condensation.[23]

The general template for enantioselective syntheses of cycloligans outlined in Figure 3 serves as the foundational touchstone for the following overviews of the various completed syntheses covered herein. We have structured the review in sections, distinguished by the different strategic disconnections used, and highlighted the variety of natural products prepared with each method. In each subsection the key disconnection related to Fig. 3 is indicated and the enantioselective process controlling asymmetric induction is highlighted. Our hope is to clearly show the creative wealth of strategies and methods that this class of natural products has inspired.

3.1.1 Disconnection A: Benzhydryl Synthon Approach I

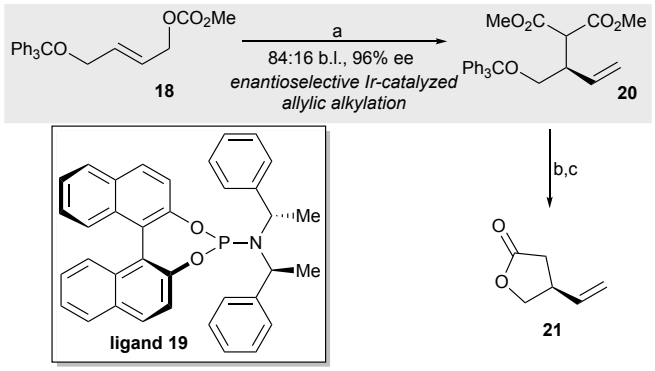
3.1.1.1 Podophyllotoxin

Bach's Synthesis: In 2008, Bach and coworkers presented the concise total synthesis of (–)-podophyllotoxin (**1**).[24] Their synthetic strategy involved the formation of a benzhydryl synthon intermediate **17**. From that key intermediate, a Heck reaction was used to close the final ring system through the formation of the C1-C7 bond (pathway ***A***, Fig. 3A) to supply the aryltetralin backbone (Scheme 3). Initially, Taniguchi lactone **21** was prepared and the authors cite two methods for its preparation: a two-step formation from 2-butyne-1,4-diol followed by optical resolution to give enantiomerically pure **21**,[25, 26] or a sequence utilizing a key iridium-catalyzed allylation as shown in Scheme 4.[27] An aldol reaction of the synthesized Taniguchi lactone **21** and 3,4,5-trimethoxybenzaldehyde

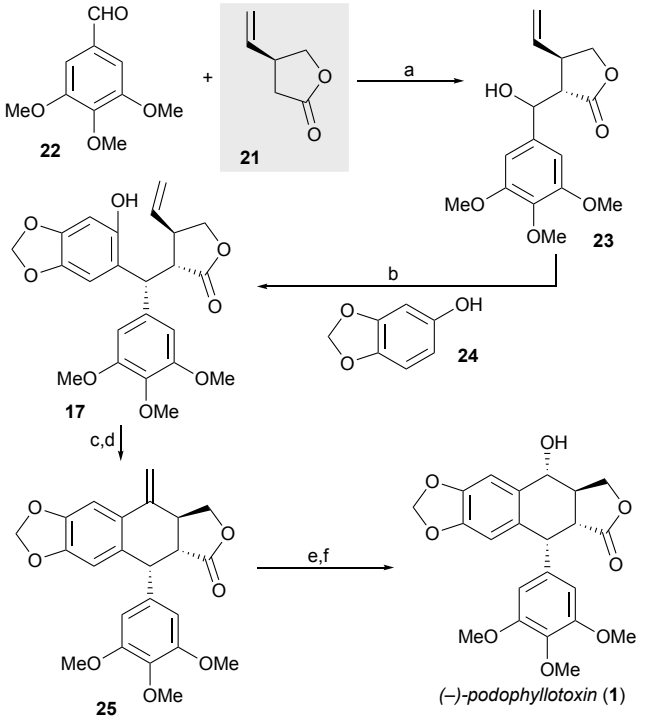


Scheme 3 Bach's synthetic strategy towards (–)-podophyllotoxin.

22 afforded trans-lactone **23** (Scheme 5). The poor diastereoselectivity at the benzyl position proved to be inconsequential, as the formed mixture of alcohols was ionized in the next step. Several Lewis acid catalysts and aryl coupling partners were screened to develop a diastereoselective Friedel–Crafts alkylation. Ultimately, treatment of **23** with $FeCl_3$ in the presence of sesamol **24** afforded benzhydryl **17**, in excellent yield and with high levels of diastereoselectivity (d.r. 94:6), elegantly setting the desired C7' stereochemistry. Triflation of **17** and subsequent intramolecular Heck reaction formed the C1–C7 bond to deliver cyclized product **25**. The exocyclic olefin within **25** was converted to the corresponding ketone through dihydroxylation and oxidative cleavage. Stereoselective reduction completed the total synthesis of (–)-podophyllotoxin (**1**) with excellent diastereoselectivity (d.r. 98:2) in six total steps from **21** and **22**.



Scheme 4 Synthesis of Taniguchi Lactone. a) $[Ir(COD)Cl]_2$ (2.0 mol%), **ligand 19** (4.0 mol%), TBD (8.0 mol%), THF, 2.5 h, then **18** (1.0 eq.), $NaCH(CO_2Me)_2$ (1.4 eq.), r.t., 96%, 84:16 d.r., 96% ee; b) NaCl (1.5 eq.), H_2O (6.2 eq.), DMSO, 160 °C, 22 h, > 99% ee; c) $ZnCl_2$ (1.1 eq.), CH_2Cl_2, r.t., 15 h, 77% over 2 steps, > 99% ee.

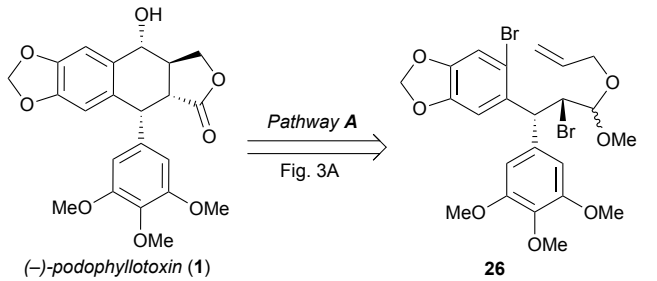


Scheme 5 Bach's total synthesis of (–)-podophyllotoxin. a) LDA (1.1 eq.), THF, –78 °C, 30 min, –78 °C, 3 h, 94%, 52:48 d.r.; b) $FeCl_3$ (5 mol%), CH_2Cl_2, 20 °C, 1 h, 99%, 94:6 d.r.; c) Tf_2O (1.5 eq.), Et_3N (2.0 eq.), CH_2Cl_2, 0 °C, 1 h, 89%; d) $Pd(OAc)_2$ (10 mol%), PPh_3 (0.3 eq.), K_2CO_3 (3.0 eq.), MeCN, 80 °C, 20 h, 58%; e) OsO_4 (5 mol%), NMO (3.0 eq.), CH_2Cl_2, 20 °C, 4 h, then, $NaIO_4$ (2.0 eq.), 30 min, 95%; f) $LiAlH(Ot\text{-}Bu)_3$ (10 eq.), Et_2O, –78 °C → 20 °C, 18 h, 79%, 98:2 d.r.

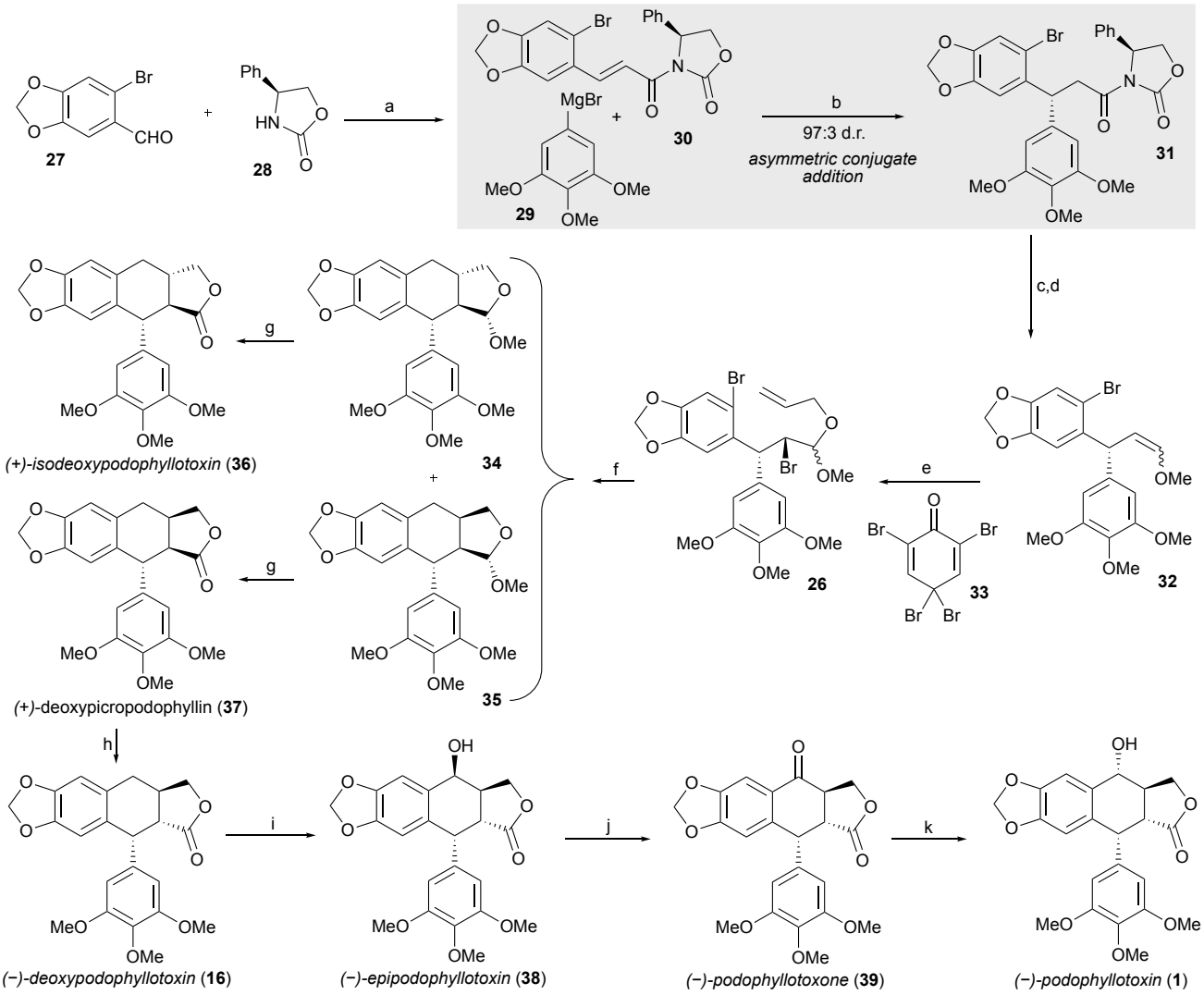
Peng's Synthesis: In 2018, Peng and coworkers developed a new synthetic route towards the synthesis of (–)-podophyllotoxin (**1**) involving a key Ni-catalyzed cyclization to form the C1–C7 and C8–C8' bonds concurrently from a benzhydryl synthon similar to pathway ***A*** as shown in Fig. 3A (Scheme 6).[28] Readily available 6-bromopiperonal **27** was converted to unsaturated imide **30** though a Horner-Wadsworth-Emmons reaction and coupling to the Evans auxiliary (*S*)-(+)-4-phenyl-2-oxazolidinone **28** (Scheme 7). An auxiliary-controlled asymmetric conjugate addition with (3,4,5-trimethoxyphenyl)-magnesium bromide **29** then delivered benhydryl **31** with excellent selectivity (d.r. 97:3). Reduction facilitated removal of the auxiliary, and subsequent oxidation and acetylization followed by elimination provided the enol ether **32**. Selective β-bromination with ketone **33** was completed to generate β-bromo acetal **26** (d.r. 1.2:1) and set the stage for a key Ni-catalyzed tandem reductive cyclization to generate diastereomeric compounds **34** and **35**. After separation through column chromatography and subsequent oxidation with PCC, (+)-isodeoxypodophyllotoxin (**36**) and (+)-deoxypicropodophyllin (**37**) were formed from **34** and **35**, respectively. (+)-Isodeoxypodophyllotoxin (**36**) could undergo lactone breakage and oxidation to form an intermediate used in the synthesis of (–)-picropodophyllin (**2**) and (–)-picropodophyllone,[29] while (+)-deoxypicropodophyllin (**37**) underwent epimerization to give (–)-deoxypodophyllotoxin (**16**), which was converted to (–)-epipodophyllotoxin (**38**) following radical bromination and hydrolysis. Oxidation of **38** generated (–)-podophyllotoxone (**39**), which was reduced stereospecifically with L-selectride to yield (–)-podophyllotoxin (**1**) in 11 steps from aldehyde **27**.

3.1.1.2 β- and γ-Apopicropodophyllins

Peng's Synthesis: Following their work developing a new synthesis of podophyllotoxin via their key Ni-catalyzed reductive tandem coupling reaction,[28] the Peng group focused their attention on expanding this approach to generate the bioactive aryldihydronaphthalene lignans (+)-β- and γ-apopicropodophyllins.[30] Their approach mirrors that employed for (–)-podophyllotoxin (**1**), involving the simultaneous formation of the C1–C7 and C8–C8' bonds most similar to pathway ***A*** shown in Figure 3A (Scheme 6). Initially, β-bromo acetal **26** (d.r. 1.2:1) was prepared according to the procedure developed during their the synthesis of (–)-podophyllotoxin (Scheme 7, 8).[28] Next, the key Ni-catalyzed



Scheme 6 Peng's synthetic strategy towards (–)-podophyllotoxin.

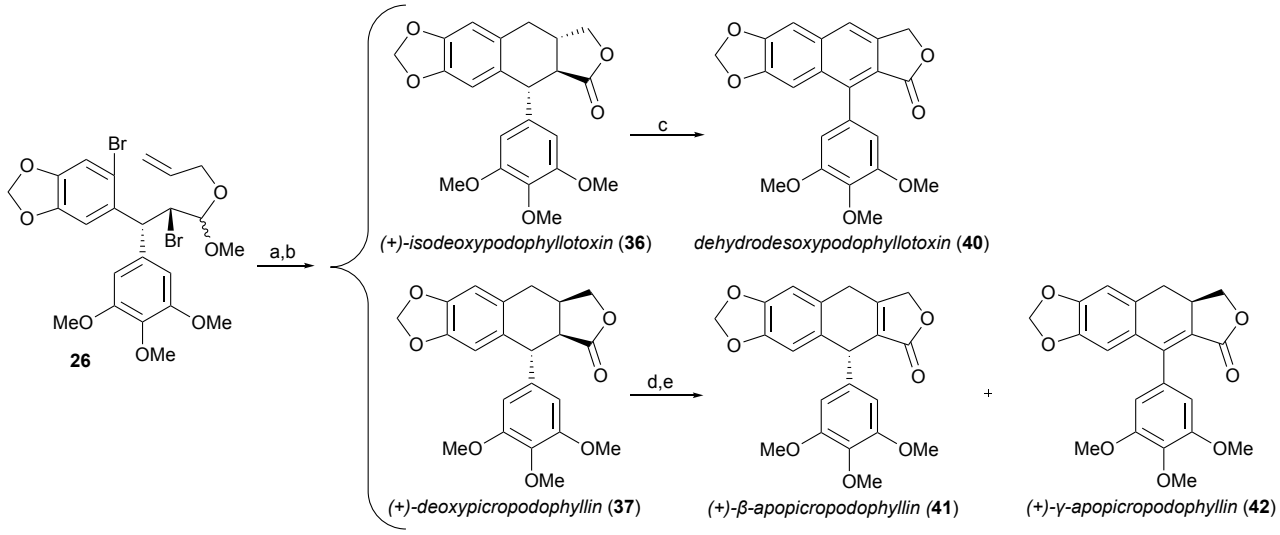


Scheme 7 Peng's total synthesis of (–)-podophyllotoxin. a) NaH (1.7 eq.), TEPA (1.7 eq.), THF, 0 °C → r.t., 3 h, then NaOH (4N), MeOH, 66 °C, 3 h, then HCl (6N), 0 °C, 5 min, then **28** (1.1 eq.), LDA (1.1 eq.), THF, –78 °C, 1 h, then Et_3N (1.2 eq.), PivCl (1.1 eq.), THF, 0 °C, 3.5 h, 94% overall; b) CuBr•SMe_2 (1.5 eq.), THF, –48 °C → 0 °C, 3.5 h, 80%, 97:3 d.r.; c) $NaBH_4$ (3.0 eq.), THF, r.t., 10 h, then PCC (1.5 eq.), CH_2Cl_2, 0 °C → r.t., 5 h, then TMOF, CSA (0.1 eq.), MeOH, 45 °C, 35 min, 88% overall; d) TMSOTf (3.0 eq.), DIPEA (3.5 eq.), CH_2Cl_2, –25 °C, 25 min, 85% brsm, 10:1 d.r.; e) allyl alcohol (20 eq.), CH_2Cl_2, 0 °C → r.t., 10 h, 76%, 1.2:1 d.r.; f) Zn (1.2 eq.), $NiCl_2$•DME (30 mol%), ethyl crotonate (0.9 eq.), pyridine, DMA, 55 °C → r.t. 4 h, **34** = 35% and **35** = 41%; g) HCl (3N), THF, r.t., 2 h, then PCC (3.0 eq.), 4 Å MS, CH_2Cl_2, 0 °C → r.t., 1.5 h, **36** = 62%, **37** = 68%; h) LDA (2.0 eq.), THF, –78 °C, 20 min, then AcOH (7.0 eq.), 93% brsm; i) NBS (1.4 eq.), 1,4-dioxane, *hν* (12 W), 20 min, 81%. j) PDC (1.5 eq.), CH_2Cl_2, 0 °C → r.t., 1 h, 90%; k) L-selectride (1.3 eq.), THF, –78 °C, 1.5 h, 87%.

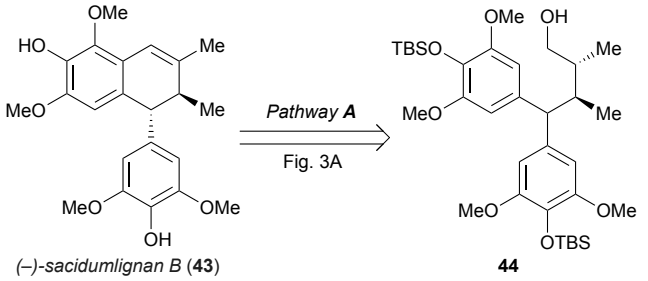
cyclization reaction was completed to diastereodivergently produce both (+)-isodeoxypodophyllotoxin (**36**) and (+)-deoxypicropodophyllin (**37**), the former of which was used to prepare achiral dehydrodesoxypodophyllotoxin (**40**). From (+)-deoxypicropodophyllin (**37**), incorporation of a C8' phenylselenyl group produced two diastereomers that were separated via column chromatography and then each subjected to *syn*-elimination via the corresponidng phenylselenoxides to deliver both (+)-β-apopicropodophyllin (**41**) and γ-apopicropodophyllin (**42**) in 9 total steps.

3.1.1.3 Sacidumlignan B

Ramana's Synthesis: Ramana and coworkers presented the syntheses of three lignans in 2012, including (–)-sacidumlignan B (**43**).[31] Their synthetic strategy involved the formation of the C1–C7 bond from a benzhydryl synthon (Scheme 9) via pathway ***A*** **(**Fig. 3A). Benzyl ester **45** was prepared according to the Evans' group published work, achieving stereoselective methylation via a chiral auxiliary.[32] Bis-addition of aryl bromide **46** to **45** furnished a benzhydryl alcohol, which upon subsequent allyl-deprotection and TBS-protection yielded benzhydryl alcohol **47** (Scheme 10). Treatment of olefin **47** with Lemieux–Johnson oxidative cleavage conditions led to the aldehyde, which subsequently cyclized to form lactol diastereomers. The diastereomers were oxidized with Celite-supported silver carbonate to the corresponding lactone, which upon diastereoselective α-methylation led to lactone **48**. Lactone **48** served as common intermediate for accessing (–)-sacidumlignan B (**43**) as well as the unusual structure of the neolignan (–)-sacidumlignan D (three steps from **48**). Reduction of lactone **48** led to a benzhydryl alcohol, which could be removed selectively by treatment with BF_3•OEt_2 and Et_3SiH to yield **44**. Oxidation of primary alcohol **44** furnished the corresponding aldehyde, which when treated with *p*-TsOH, underwent a diastereoselective cyclization followed by elimination to yield a dihydronaphthalene by forming a bond between the C1 and C7 positions. Final TBS deprotection of that compound completed the total synthesis of (–)-sacidumlignan B (**43**).

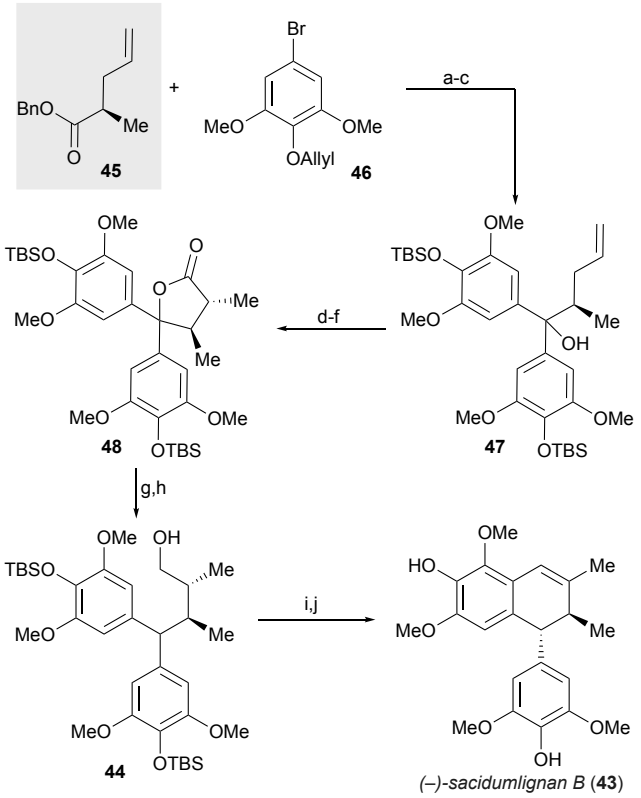


Scheme 8 Peng's total synthesis of β- and γ-Apopicropodophyllins. a) Zn (1.2 eq.), $NiCl_2$•DME (30 mol%), ethyl crotonate (0.9 eq.), pyridine, DMA, 55 °C → r.t. 4 h; b) HCl (3 N), THF, r.t., 2 h, then PCC (3.0 eq.), 4 Å MS, CH_2Cl_2, 0 °C → r.t., 1.5 h, **36** = 62%, **37** = 68%; c) NBS (1.0 eq.), BPO (0.1 eq.), CCl_4, 82 °C, 2 h, 56%; d) LDA (2.0 eq.), PhSeBr (2.0 eq.), THF, –78 °C, 40 min, **41** = 65%, **42** = 30%; e) *m*-CPBA (2.0 eq.), $NaHCO_3$ (2.0 eq.), CH_2Cl_2, 0 °C, 15 min, 88%.



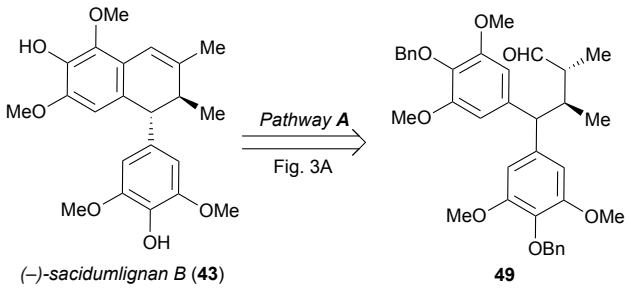
Scheme 9 Ramana's strategy towards (–)-sacidumlignan B.

Peng's Synthesis: Peng and coworkers developed a synthetic method for the formation of N,N-dimethyl-4,4-diaryl-butanamides through a base-promoted addition of dimethylacetamide (DMA) with 1,1-diarylethylenes, and applied it to the total synthesis of (–)-sacidumlignan B (**43**).[33] This was a continuation of their work in 2013 in the synthesis of sacidumlignan A and racemic sacidumlignan D via an Ueno–Stork radical cyclization reaction.[34] The synthetic strategy utilized involved a benzhydryl synthon and a key C1–C7 bond-forming cyclization (Scheme 11), thus utilizing pathway ***A*** (Fig. 3A). Arylbromide **50** went through lithium-bromine exchange following treatment with *n*-butyllithium, and after addition of acetyl chloride and subsequent dehydration, generated 1,1-diarylethylene **51** (Scheme 12). DMA was added according to their optimized reaction conditions to prepare amide intermediate **52**. Addition of KOH, followed by HCl produced carboxylic acid **53** and was then converted into a mixed anhydride upon addition of pivaloyl chloride and triethylamine. Adding ***ent*-28** generated oxazolidinone **54**, which went through deprotonation, selenation, and oxidative addition to generate alkene **55**. This compound subsequently underwent conjugate addition and methylation to produce oxazolidinone **56** with excellent diastereoselectivity (d.r. 94:6), which was converted into the acid and subsequently reduced to an alcohol. Aldehyde **49** was formed after oxidation with DMP, and hydrogenation

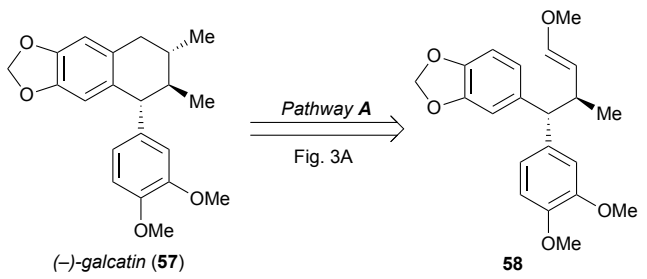


Scheme 10 Ramana's total synthesis of (–)-sacidumlignan B. a) *n*-BuLi (2.1 eq.), THF, –78 °C, 2 h, 63%; b) $Pd(OAc)_2$ (4 mol%), PPh_3 (8 mol%), *N,N*-DMBA (2.2 eq.), EtOH, r.t., 2 h, 84%; c) TBSCl (2.5 eq.), imidazole (4.0 eq.), DMF, r.t., 1 h, 96%; d) OsO_4, $NaIO_4$ (1.5 eq.), 2,6-lutidine (2.0 eq.), 1,4-dioxane. water, r.t., 2 h, 84%; e) Ag_2CO_3-Celite (5.0 eq.), PhMe, reflux, 2 h, 92%; f) *n*-BuLi (3.0 eq.), HMDS (4.0 eq.), THF, –78 °C, 30 min, then MeOTf (1.5 eq.), –78 °C, 4 h, 94%; g) $LiAlH_4$ (3.0 eq.), THF, 0 °C → r.t., 30 min; h) Et_3SiH (5.4 eq.), BF_3• OEt_2 (3.1 eq.), CH_2Cl_2, 0 °C, 5 min, 74% over 2 steps; i) IBX (1.3 eq.), EtOAc, reflux, 1 h; j) *p*-TsOH (5 mol%), PhMe, r.t., 15 min, 80% over 2 steps; k) TBAF (2.3 eq.), THF, 0 °C, 30 min, 95%.

yielded the phenol, which afforded (–)-sacidumlignan B (**43**) after acidic treatment in 14 linear steps.



Scheme 11 Peng's synthetic strategy towards (–)-sacidumlignan B.



Scheme 13 Thomson's synthetic strategy for cyclolignan products.

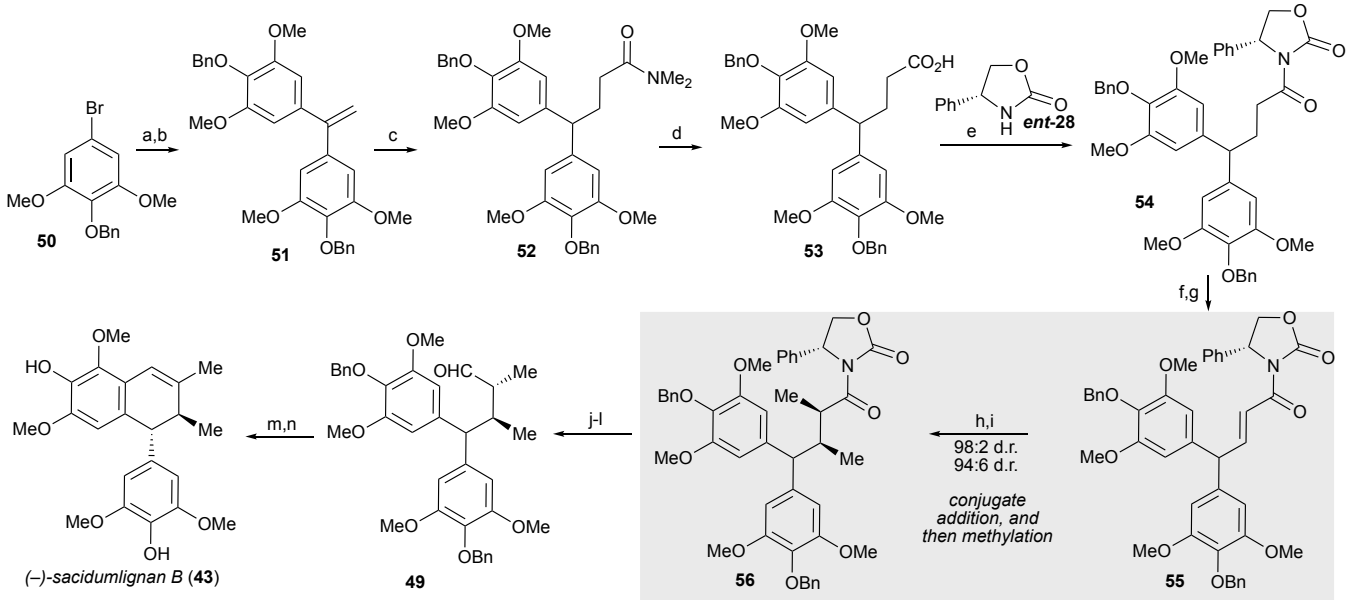
3.1.1.4 Three Hydronaphthalene and Three Tetralone Lignans

Thomson's Synthesis: In 2014, Thomson and coworkers published the total synthesis of six lignan natural products that represented potential anti-malarial drug candidates.[35-40] They developed a stereoselective fragment-coupling reaction that would incorporate the aryl groups and subsequently generate the C7' and C8' stereocenters via a *N*-allylhydrazone cascade process.[40, 41] The final synthetic strategy involved a key C1–C7 bond formation through a stereoselective cyclization process from a benzhydryl synthon (Scheme 13), thus utilizing pathway ***A*** (Fig. 3A). Hydrazone **61** was prepared from starting aldehyde **60** and optically enriched hydrazine fragment **59** (Scheme 14).[42, 43] A one-pot oxidative [3,3] rearrangement and Friedel-Crafts arylation with aryl **62** generated benzhydryl **63**. Oxidative alkene cleavage and Wittig olefination yielded methyl enol ether **58**. Treatment with trifluoroacetic acid followed by oxidation with IBX and subsequent methylation generated (–)-8'-epi-aristotetralone (**68**), (–)-8'-epi-aristoligone (**69**), or (–)-4'-O-methylenshicine (**64**) in eight steps each with 28%, 43%, or 24% total isolated yields respectively (d.r. 3:1). Methyl enol ether **58** was cyclopropanated according to Shi's conditions,[44] and was subsequently heated in acidic conditions to give (–)-cyclogalgravin (**67**) or (–)-pyananthulignene B (**66**) in seven steps each. Finally, (–)-galcatin (**57**) was prepared following hydrogenation of **65** in eight total steps (d.r. 16:1).

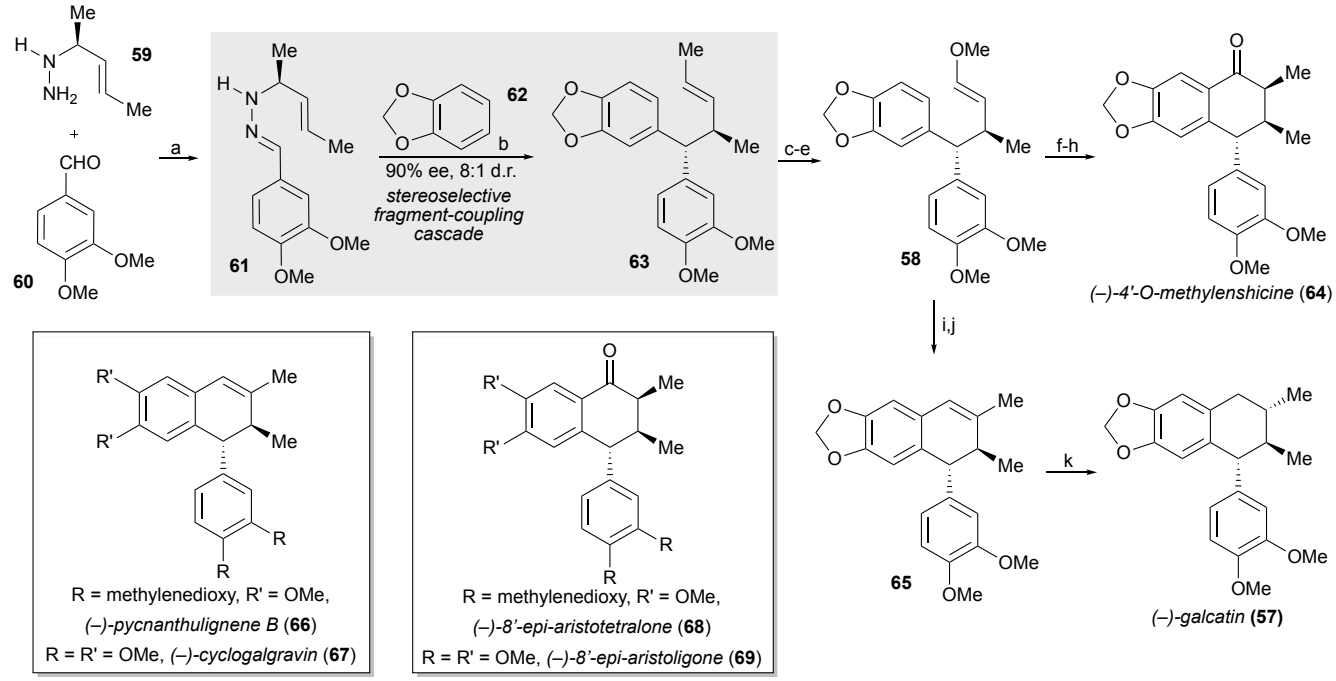
3.1.2 Disconnection B: Benzhydryl Synthon Approach II

3.1.2.1 Podophyllotoxin

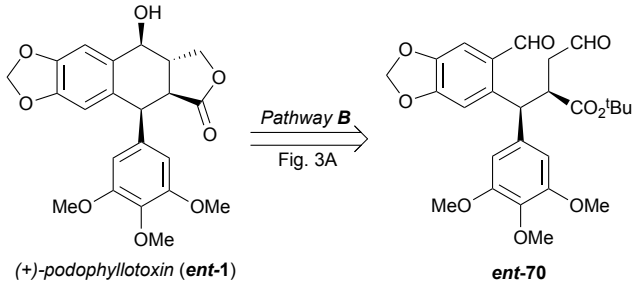
Zhang's Synthesis: In 2007, Zhang and coworkers reported the total synthesis of racemic podophyllotoxin using a key conjugate addition/enolate alkylation cascade reaction.[45] In 2009, they reported an enantioselective variation which enabled the total synthesis of (+)-podophyllotoxin (***ent*-1**). Their retrosynthetic strategy involved a key C7–C8 disconnection through pathway ***B*** (Fig. 3A) to the benzhydryl synthon (Scheme 15).[46] To render their methodology enantioselective, (+)-pseudoephedrine-derived oxazolidine **71** was used for the Michael donor, which doubled as a protecting group (Scheme 16). The aryl lithium reagent was pre-formed by treating **71** with *n*-butyl lithium before addition to *tert*-butyl ester **72**. The enolate was trapped with allylbromide and the resulting oxazolidine was hydrolyzed to yield aldehyde **73** with the desired *cis*-stereochemistry (99% ee). Terminal olefin **73** was oxidatively cleaved in a two-step procedure to yield the bisaldehyde ***ent*-70**. L-Proline-catalyzed intramolecular aldol reaction of ***ent*-70** resulted in two alcohol diastereomers, which were subsequently oxidized to yield tetralone **74** as a single



Scheme 12 Peng's total synthesis of (–)-sacidumlignan B. a) *n*-BuLi (1.0 eq.), AcCl (0.4 eq.), THF, –78 °C → r.t., 9.5 h; b) PTSA•H_2O (0.2 eq.), PhMe, 45 °C, 5 h, 48% over 2 steps; c) NaHMDS (1.5 eq.), DMA, r.t., 3 h, 71%; d) KOH (5.0 eq.), EtOH, H_2O, then HCl (1N), 70 °C, 7 d, 73%; e) PivCl (1.2 eq.), Et_3N (2.4 eq.), DMAP, CH_2Cl_2, 35 °C, 8 h, 90%; f) LDA (1.2 eq.), PhSeBr (1.2 eq.), THF, –78 °C → r.t., 9.5 h; g) *m*-CPBA (0.7 eq.), CH_2Cl_2, r.t., 15 min, 60% over 2 steps; h) CuBr•SMe_2 (2.0 eq.), MeMgBr, –45 °C → r.t., 9.5 h, 75%; i) NaHMDS (1.5 eq.), CH_3I (1.5 eq.), THF, –45°C→ r.t., 9.5 h, 66%, 94:6 d.r.; j) LiOH, H_2O_2, THF, H_2O, 0 °C → r.t. 10 h; k) $LiAlH_4$ (0.75 eq.), THF, 0 °C, 15 min, 74% over 2 steps; l) DMP (1.5 eq.), CH_2Cl_2, 0 °C, 2 h, 91%. m) Pd/C (10%), H_2, EtOH, r.t., 5 h; n) PTSA•H_2O (0.5 eq.), PhMe, r.t., 2 h, 83% over 2 steps.



Scheme 14 Thomson's synthesis of key intermediate for cyclolignan total syntheses. a) K_2CO_3 (1.5 eq.), MeOH, r.t., 12 h, 95:5 e.r.; b) $PhI(OTf)_2$ (1.0 eq.), TFA (25 eq.), MeOH, –78 °C → 0 °C, 4 h, 66%, 95:5 e.r., 8:1 d.r.; c) OsO_4 (1 mol%), NMO (3.0 eq.), H_2O, 1,4-dioxane, r.t., 24 h; d) $NaIO_4$ (1.0 eq.), MeOH, H_2O, r.t., 5 h, 84% over 2 steps; e) $[Ph_3PCH_2OMe]^+ Cl^-$ (1.7 eq.), NaHMDS (1.7 eq.), Et_2O, 0 °C, 4 h, 99%; f) TFA (1.0 eq.), THF, H_2O, r.t., 48 h, 79%; g) MnO_2 (15 eq.), THF, r.t., 36 h, 73%; h) LiHMDS (5.0 eq.), MeI (40 eq.), THF, –78 °C → r.t., 12 h, 94%, 3:1 d.r.; i) Et_2Zn (3.0 eq.), CH_2I_2 (3.0 eq.), TFA (3.0 eq.), CH_2Cl_2, 0 °C → r.t., 4.5 h, 78%; j) HCl, MeOH, reflux, 1 h, 97%; k) Pd/C (10 mol%), H_2, EtOH, r.t., 24 h, 89%, 16:1 d.r.



Scheme 15 Zhang's synthetic strategy towards (+)-podophyllotoxin.

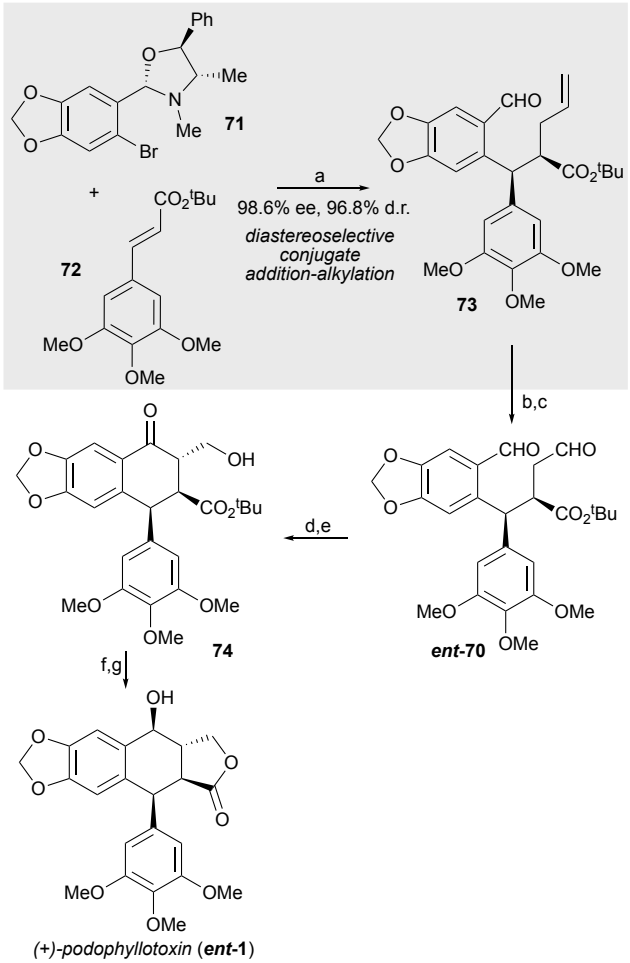
isomer. Acid-catalyzed lactonization of **74** followed by selective reduction of the ketone completed the total synthesis of (+)-podophyllotoxin (***ent*-1**) as a single isomer with an overall yield of 29% in eight steps.

Ishikawa's Synthesis: In 2013, the Ishikawa lab published a formal synthesis of **1** where they targeted both the enantiomer of Zhang's intermediate **70** (Scheme 17), as well as Meyers' 4-aryl-1-tetralone-lactone **81**,[29,46] (Scheme 18) utilizing a diastereoselective aziridine ring opening as their key step.[47] Both of these methods uses a synthetic strategy most similar to that shown in pathway ***B*** (Fig. 3A). Aziridine **76** was prepared with absolute and relative stereocontrol using Ishikawa's previously developed methodology for the synthesis of 3-arylaziridine-2-carboxylates from (*R,R*)-guanidinum salt **75** and commercially available 3,4,5-trimethoxybenzaldehyde **22** with 82% ee.[48] The chiral salt **75** was synthesized in 3-steps using their methodology published in 1998, starting from commercially available (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine.[49] A screen of various Lewis acids allowed the authors to optimize the diastereoselectivity of the ring-opening reaction from 4:1 with $InCl_3$, to an enhanced 10:1 of sesamol-inserted 2-amino-3-arylpropanoate **77** with $Zn(OTf)_2$. Benzhydryl **77** was then transformed into common key precursor **78** with conservation of enantiopurity. On one hand, precursor **78** was used in the synthesis of the enantiomer of Zhang's intermediate, **70**, with an overall yield of 26% in eight steps. On the other hand, the treatment of compound **78** with NIS and protection of the alcohol gave iodohydrin **79**. This allowed them to generate the C8-C8' bond in three steps making tetralone **80**, which went through an aldol condensation reaction with formaldehyde to give Meyers' intermediate **81** with an overall yield of 35% in eleven steps from **22** and **75**.

3.1.3 Disconnection C: The Naphthyl and Aryl Synthon Approach

3.1.3.1 Podophyllotoxin

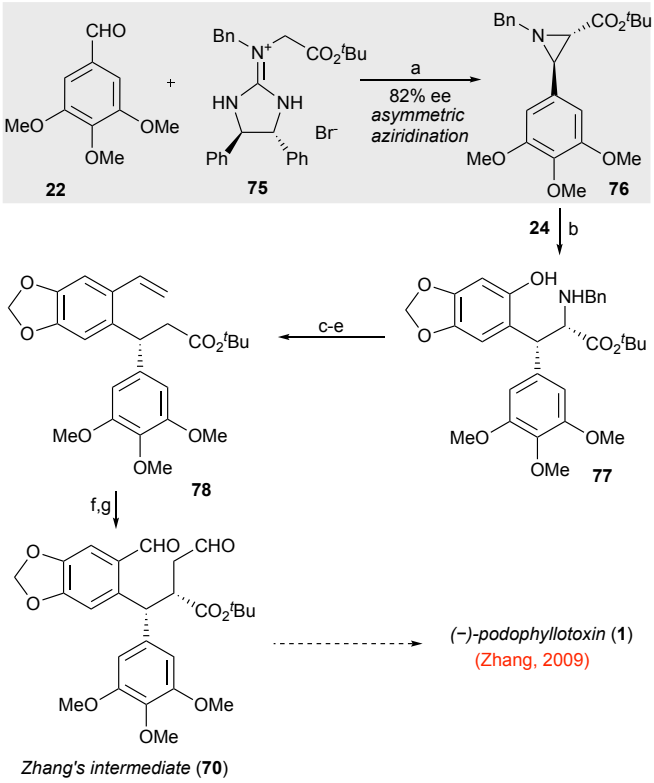
Berkowitz's Synthesis: Berkowitz and coworkers reported the total synthesis of (–)-podophyllotoxin (**1**) and its C4 epimer, (–)-picropodophyllin (**2**) in 2000.[50] Their retrosynthetic strategy followed pathway ***C*** (Fig. 3A), thus involving the key bond disconnection between C1' and C7' to yield naphthyl and aryl synthons (Scheme 19). This was done so as to introduce the lower aryl system as late as possible in the syntheses, and facilitate catalytic control of absolute stereochemistry, which differed from previous approaches towards podophyllotoxin.[29, 51-54] They employed an enzymatic desymmetrization of diacetate **83** (constructed in seven steps from piperonal) with porcine pancreatic lipase (PPL) to achieve an asymmetric synthesis with excellent selectivity (95% ee) (Scheme 20). Monoacetate **84** was transformed into dihydronaphthalene **82** through functional group interconversions and a key retro-Michael ring opening, and then a chiral auxiliary was subsequently added to form **85**. Though the authors initially had difficulty with aromatization of the dihydronaphthalene functionality, the final ring of **1** was installed successfully installed through an aryl cuprate addition of **29** to oxazolidinone **85**. Formation of the lactone proceeded smoothly through desilylative lactonization to yield the pentacyclic core **86**. An epimerization of *cis*-lactone **86** to the



Scheme 16 Zhang's total synthesis of (+)-podophyllotoxin. a) *n*-BuLi (2.0 eq.), THF, then TMEDA (2.0 eq.), –78 °C, 2 h, then allyl bromide (5.0 eq.), r.t., 2 h, then AcOH/H_2O (1:1) in THF, r.t., 12 h, 65%; b) OsO_4 (10 mol%), NMO (2.0 eq.), *t*-BuOH, THF, H_2O, r.t.; c) $NaIO_4/SiO_2$ (1 mmol/2 g, 1.0 eq.), CH_2Cl_2, r.t., 3 h, 94% over 2 steps; d) L-proline (10 mol%), CH_2Cl_2, r.t., 4 h, then $NaBH_4$ (1.2 eq.), MeOH, 0 °C, 30 min, 80%; e) MnO_2 (10 eq.), MeCN, r.t., 2-3 days, 81%; f) HCl (37%), MeCN, r.t., 4 h, then DCC (1.0 eq.), CH_2Cl_2, r.t., 10 min, 90%; g) L-selectride (1.3 eq.), THF, –78 °C, 2 h, 98%, 99% ee.

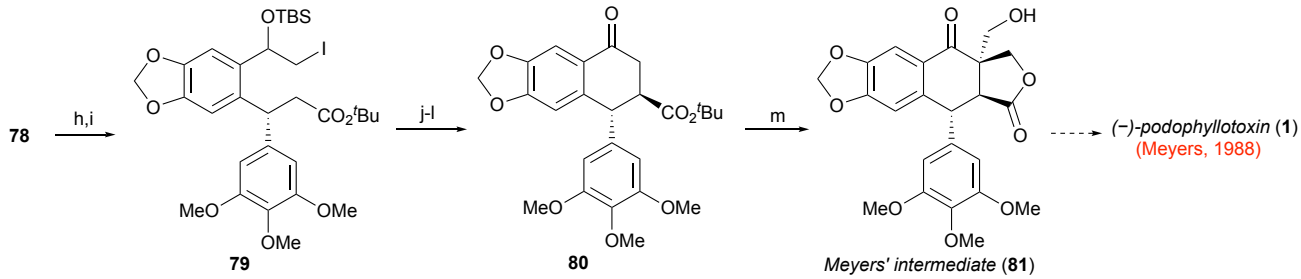
thermodynamically less-favorable *trans*-lactone of **1** was required before SEM deprotection to complete the total synthesis of (–)-podophyllotoxin (**1**). Simple SEM deprotection of **86** completed the total synthesis of (–)-picropodophyllin (**2**).

Sherburn's Synthesis: During their work on the synthesis of gibberellin natural products, Sherburn and Mander observed an unexpected carboxyarylation product in their attempts to conduct a

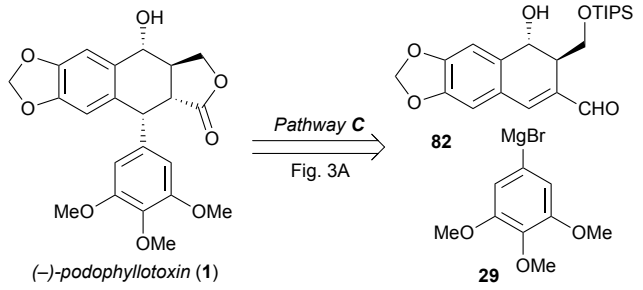


Scheme 17 Ishikawa's formal synthesis of (–)-podophyllotoxin from Zhang's intermediate. a) TMG (1.0 eq.), THF, 0 °C → r.t., 24 h, then SiO_2, $CHCl_3$, r.t., 24 h, 84%, 82% ee; b) $Zn(OTf)_2$ (10 mol%), CH_2Cl_2, 30 °C, 9 h, 89%, 10:1 d.r.; c) SmI_2 (4.8 eq.), HMPA (4.8 eq.), H_2O (6.6 eq.), THF, r.t., 1 h, 93%; d) Tf_2O (1.5 eq.), pyridine (3.2 eq.), CH_2Cl_2, –40 °C → 0 °C, 1 h, 92%; e) Tributyl(vinyl)tin (1.3 eq.), $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (10 mol%), LiCl (2.0 eq.), DMF, 50 °C, 7 h, 90%, 99% ee; f) allyl bromide (3.0 eq.), LiHMDS (2.1 eq.), THF, –78 °C → r.t., 4 h, 92%, 3:1 d.r.; g) OsO_4 (10 mol%), $NaIO_4$ (6.0 eq.), dioxane, H_2O, 50 °C, 8 h, 49%.

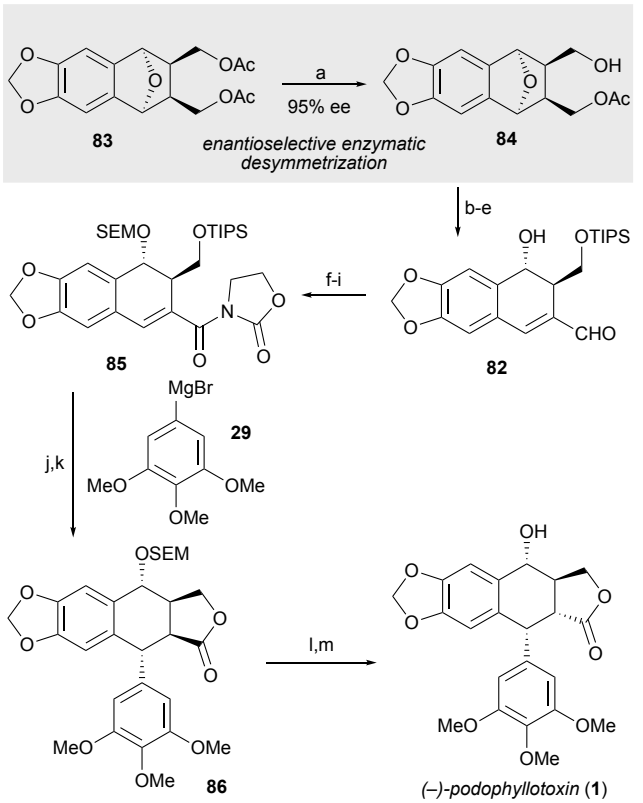
Barton–McCombie radical deoxygenation.[55] In 2003, Sherburn and coworkers utilized this reaction as a key step in their approaches to the total synthesis of (–)-podophyllotoxin (**1**) and (+)-podophyllotoxin (***ent*-1**), forming the C1'–C7' bond (pathway ***C***, Fig. 3A) and finishing the construction of the aryltetralin backbone (Scheme 21).[56] In both approaches, they targeted the natural product isopicropodophyllone[57] (***ent*-93**) through a thionocarbonate intermediate, which could then be converted to a hydroxyl ester through methanolysis and subsequently transformed to **1** through a sequence similar to that used by Bush in his total synthesis.[51] The key thionocarbonate intermediate was prepared two different ways, by using an Evans aldol ring-closing metathesis to give (+)-



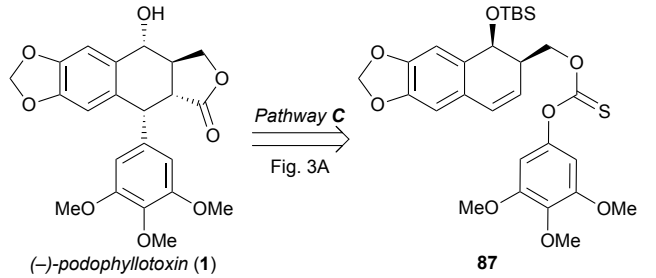
Scheme 18 Ishikawa's formal synthesis of (–)-podophyllotoxin from Meyers' intermediate. h) NIS (1.2 eq.), THF, H_2O, r.t., 7 h, 95%, 2:1 d.r.; i) TBSOTf (1.5 eq.), 2,6-lutidine (3.0 eq.), CH_2Cl_2, r.t., 8 h, 92%, 2:1 d.r.; j) LiHMDS (1.7 eq.), HMPA (3.0 eq.), THF, –78 °C, 10 h, 90%, 2:1 d.r.; k) TBAF (2.0 eq.), THF, r.t., 8 h, 90%, 2:1 d.r.; l) DMP (1.0 eq.), $NaHCO_3$ (2.6 eq.), CH_2Cl_2, r.t., 3 h, 92%, 99% ee; m) CH_2O (37%), NaOH (2.1 eq.), THF, r.t., 24 h, 95%.



Scheme 19 Berkowitz's synthetic strategy towards (–)-podophyllotoxin



Scheme 20 Berkowitz's total synthesis towards (–)-podophyllotoxin. a) porcine pancreatic lipase, 10% DMSO, 50 nM KPO_4, pH 8, r.t., 2.5 h, 66%, 83% brsm, 95% ee; b) TIPSCl (1.1 eq.), imidazole (2.2 eq.), DMF, 0 °C → r.t., 7 h; c) K_2CO_3 (0.2 eq.), MeOH, Dowex 50x8 resin, r.t., 2 h, 97% over 2 steps; d) $(COCl)_2$ (1.7 eq.), DMSO (2.0 eq.), Et_3N (3.4 eq.), CH_2Cl_2, –78 °C → 40 °C, 2 h, 100%; e) NaOMe, MeOH, 90%; f) SEMCl (1.5 eq.), DIPEA (3.0 eq.), CH_2Cl_2, 0 °C → r.t., 12 h, 93%; g) $NaClO_2$ (9.2 eq.), NaH_2PO_4, *t*-BuOH, 2-methyl-2-butene, H_2O, r.t., 12 h, 100%; h) CDI (1.1 eq.), THF, r.t., 3 h; i) 2-oxazolidinone (1.3 eq.), *n*-BuLi (1.3 eq.), THF, –78 °C, 1 h, 64% over 2 steps; j) CuCN (8.0 eq.), THF, 10 °C, 3.5 h, 85%; k) TBAF (2.5 eq.), THF, 50 °C, 5 h, 62%; l) LDA (3.0 eq.), THF, 0 °C → –78 °C, 1.5 h, then pyr•HCl (7.0 eq.), 47% (46% of SM recovered); m) EtSH (4.5 eq.), $MgBr_2$•OEt_2 (2.3 eq.), Et_2O, PhH, 0 °C → r.t., 12 h, 81%.



Scheme 21 Sherburn's synthetic strategy towards (–)- and (+)-podophyllotoxin.

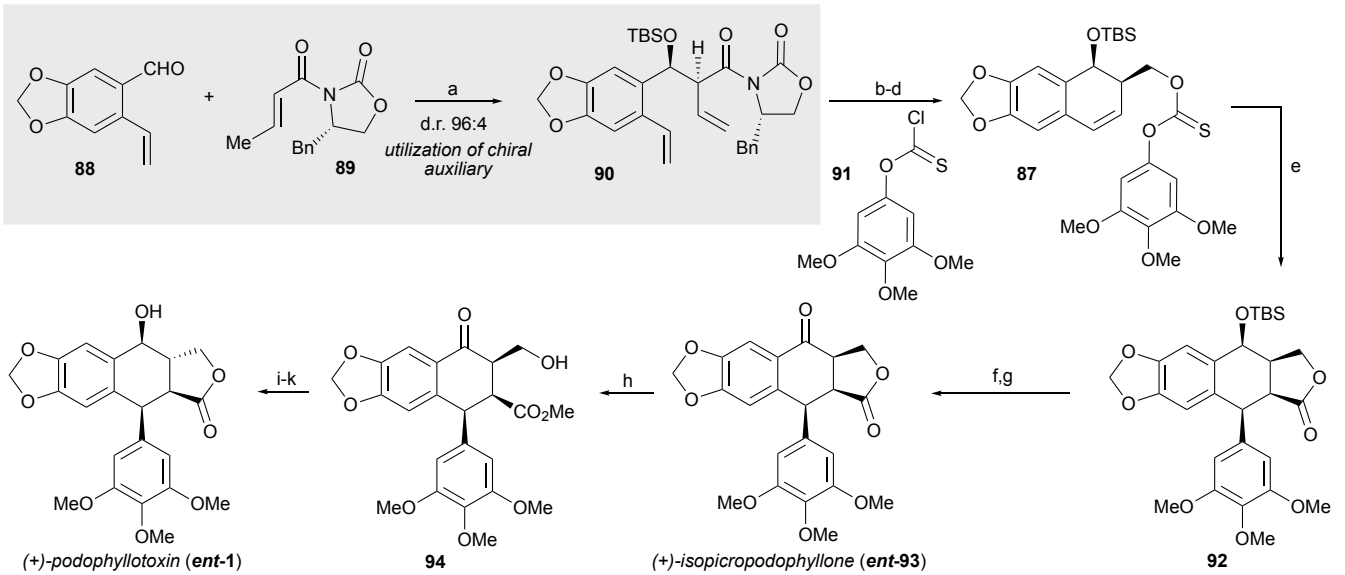
podophyllotoxin (***ent*-1**), or a Meyers' nucleophilic addition to naphthyl oxazoline to give (–)-podophyllotoxin (**1**).

In their first route (Scheme 22), the Sherburn group employed an asymmetric Evans *syn*-aldol reaction between the commercially available aldehyde **88** and imide **89** to furnish **90** with excellent selectivity (d.r. 96:4). The auxiliary was cleaved reductively and the resulting diene was treated with Grubbs catalyst to form the C2–C7' bond through ring-closing metathesis. Exposure of the free alcohol to the aryl chlorothionoformate **91** afforded thionocarbonate **87**. Treatment of **87** with $(Me_3Si)_3SiH$ and AIBN initiated the intramolecular alkene carboxyarylation to form the lactone and generate the C1'–C7' bond, while forming two new stereocenters in compound **92**. Simple deprotection and oxidation afforded (+)-isopicropodophyllone (***ent*-93**). Methanolysis of ***ent*-93** gave hydroxyl ester **94**, which was subsequently selectively epimerized at C7. Stereoselective reduction of the ketone, followed by trans-lactone formation completed the total synthesis of (+)-podophyllotoxin (***ent*-1**) in 11 steps.

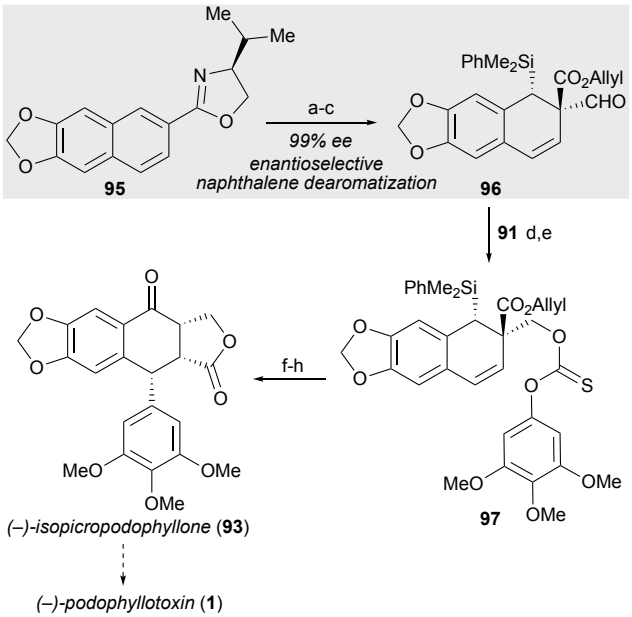
In their approach to (–)-podophyllotoxin (**1**) (Scheme 23), the Sherburn lab utilized Meyers' naphthalene dearomatization chemistry[29] to render the synthesis enantioselective. Subsequent transformation of the oxazoline **95** to the aldehyde afforded dihydronaphthalene **96**. Aldehyde **96** was in turn reduced and converted to a thionocarbonate **97** as before. The same conditions were used to initiate the intramolecular alkene carboxyarylation to complete the pentacyclic aryltetralin core. Tamao–Fleming oxidation of the silane and oxidation of the resulting alcohol furnished the ketone. Palladium(0)-mediated deallylation-decarboxylation completed their second total synthesis of (–)-isopicropodophyllone (**93**) and therefore the formal synthesis of (–)-podophyllotoxin (**1**).

3.1.3.2 Epipodophyllotoxin

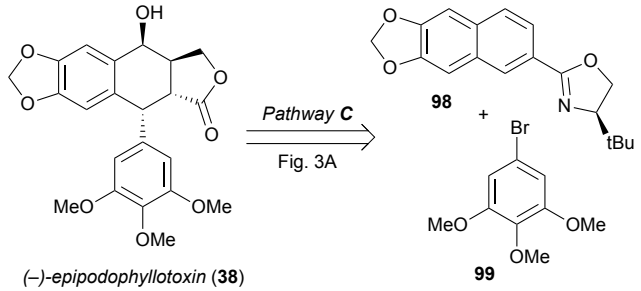
Linker's Synthesis: (–)-Epipodophyllotoxin (**38**), an epimer of (–)-podophyllotoxin (**1**) at the hydroxyl carbon position,[58] is structurally similar to the clinical antitumor drugs etoposide (**3**) and teniposide,[59-62] and therefore was an interesting target for the Linker group. In 2003, Linker and coworkers developed a synthetic strategy involving the coupling of aryl synthons to form the C1'–C7' bond in the arylnaphthalene backbone through pathway ***C*** as shown in Figure 3A (Scheme 24).[63] Naphthalene **102** was prepared from piperonal **100** following annulation with nitrile **101** (Scheme 25). Formation of chiral oxazolidinone **98** through condensation with amino alcohol 103 set the stage for the key bond forming event to generate the C1'–C7' linkage. Accordingly, trimethoxy-phenyllithium was generated in situ from bromide **99**, which underwent a diastereoselective dearomatizing addition to furnish ester **104** after methanolysis of the auxiliary. Diastereoselective oxidation was achieved through an epoxide intermediate to generate allylic alcohol **105** (96% ee). A silicon tether was used to add a hydroxymethylene group which cyclized to form the requisite lactone and thus generate (–)-epipodophyllotoxin (**38**) with excellent selectivity in 12 steps and a final 30% isolated yield.



Scheme 22 Sherburn's total synthesis of (+)-podophyllotoxin. a) *n*-Bu_2BOTf (1.3 eq.), Et_3N (1.7 eq.), CH_2Cl_2, –78 °C → 0 °C, 1 h, then H_2O_2, pH 7.2 buffer, Et_2O, r.t., 14 h, then TBSOTf (1.0 eq.), 2,6-lutidine (1.5 eq.), CH_2Cl_2, r.t., 30 min, 78%, 96:4 d.r.; b) $NaBH_4$ (15 eq.), THF, H_2O, r.t., 12 h, 94%; c) Grubbs catalyst (0.1 eq.), CH_2Cl_2, r.t., 2 h, 91%; d) pyridine (4.0 eq.), CH_2Cl_2, r.t., 2.5 h, 89%; e) $(Me_3Si)_3SiH$ (1.1 eq.), AIBN (0.5 eq.), PhH, 80 °C, 8 h, 38%; f) *n*-Bu_4NF (10 eq.), AcOH (10 eq.), THF, r.t., 8 h, 96%; g) PCC (5.0 eq.), CH_2Cl_2, 25 ºC, 5 h, 100%; h) MeOH, H_2SO_4 (4.0 eq.), r.t., 2 h, 89% brsm; i) DBU (1.0 eq.), THF, r.t., 6 h, 92%; j) $LiEt_3BH$ (1.0 eq.), THF, –78 °C, 1 h, then SiO_2, MeOH, 56 °C, 2 h, 96%; k) $ZnCl_2$ (2.0 eq.), 4 Å MS, THF, 66 °C, 2.5 h, 81%.



Scheme 23 Sherburn's synthesis of (–)-isopricropodophyllone. a) $PhMe_2SiLi$ (5.0 eq.), THF, –78 °C, 3 h, then allylchloroformate (7.5 eq.), –78 °C → r.t.; b) $KHCO_3$ (0.7 eq.), K_2CO_3 (2.5 eq.) MeOH, H_2O, 25 °C, 55 min, 57% over 2 steps; c) MeOTf (2.0 eq.), CH_2Cl_2, 25 °C, 2 h, then $NaBH_4$ (4.0 eq.) THF, MeOH, 25 °C, 30 min, then $(COOH)_2 \bullet 2H_2O$ (5.1 eq.), THF, H_2O, r.t., 16 h, 100% over 3 steps; d) Bu_3SnH (2.0 eq.), SiO_2, PhMe, 80 °C, 10 h, 79%; e) pyridine (2.0 eq.), CH_2Cl_2, r.t., 2 h, 99%; f) $(Me_3Si)_3SiH$ (1.1 eq.), AIBN (0.6 eq.), PhH, 80 °C, 14 h, 40%; g) $BF_3 \bullet 2AcOH$ (9.0 eq.), CH_2Cl_2, sealed tube, 50 °C, 27 h, then *m*-CPBA (6.9 eq.), KF (1.2 eq.), DMF, r.t., 1 h, then DMP (1.8 eq.), CH_2Cl_2, r.t., 30 min, 60% brsm over 3 steps; h) $Pd(OAc)_2$ (4.0 eq.), PPh_3 (8.0 eq.), HCOOH (40 eq.), Et_3N (50 eq.), THF, r.t., 43 min, 100%

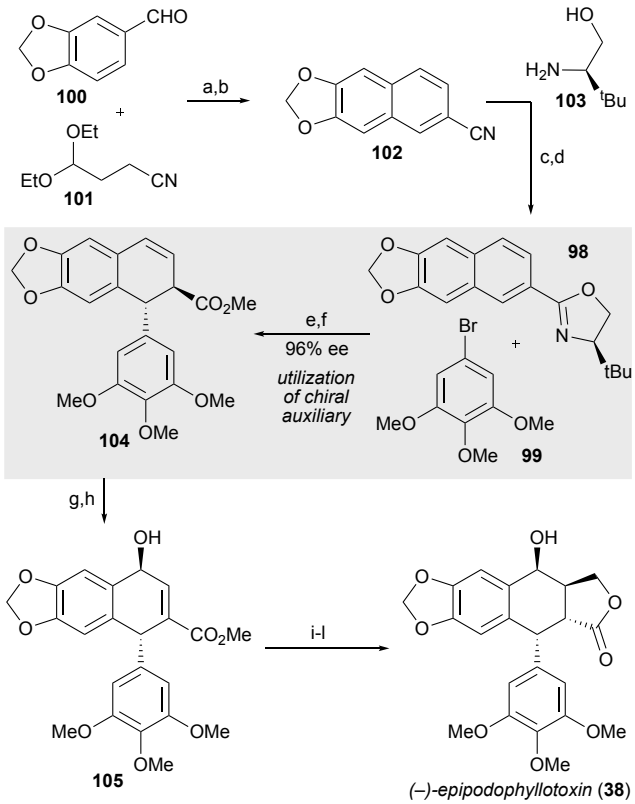


Scheme 24 Linker's synthetic strategy towards (–)-epipodophyllotoxin.

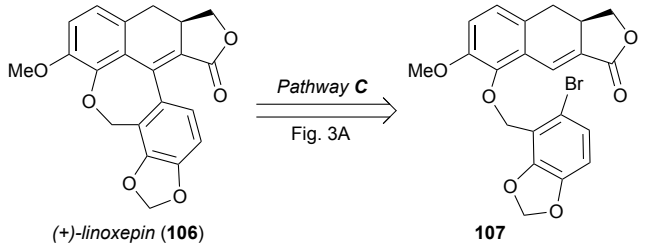
3.1.3.3 Linoxepin

Lautens' Synthesis: Lautens and coworkers reported the first enantioselective total synthesis of (+)-linoxepin (**106**) in 2013.[64, 65] They exploited the unusual C3–C2' linkage of **106** to act as a tether for the two aryl rings at the beginning of their synthesis, setting the stage for an intramolecular Mizoroki–Heck reaction later on to form the major C1'–C7' (pathway ***C***, Fig. 3A) bond from a diarylbutane synthon (Scheme 26). The key step in this synthesis was the norbornene-assisted Catellani reaction, one of the few multi-component fragment coupling reactions that forms multiple carbon–carbon bonds.[66] Enantioenriched iodolactone **111** was prepared according to the Zutter procedure utilizing enantioenriched epoxide 108 as a starting material (Scheme 27), then aryl iodide **112**, vinyl ester **113**, and the enantioenriched iodide **111** were coupled in the key Catellani reaction to form unsaturated ester **114** in excellent yield (Scheme 28). Treatment of olefin **114** with Lemieux–Johnson conditions furnished an aldehyde, which underwent a subsequent $TiCl_4$ mediated aldol-condensation to form dihydronaphthalene **107**. Exposure of this aryl bromide to Mizoroki–Heck conditions completed a concise and convergent synthesis of (+)-linoxepin (**106**) with an overall isolated yield of 30%.

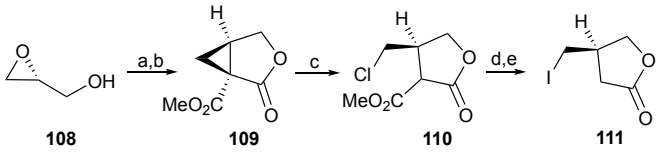
Nagasawa's Synthesis: In 2015, Nagasawa and coworkers developed an organocatalytic oxidative kinetic resolution of β- and γ-substituted tetralone derivatives,[67] which they utilized in a convergent total synthesis of (+)-linoxepin (**106**). Their synthetic strategy involved coupling naphthyl and aryl synthons with a key



Scheme 25 Linker's synthesis of (–)-epipodophyllotoxin. a) LDA, –78 °C, 1 h; b) H_2SO_4 (20%), MeOH, 65 °C, 1.5 h, 94%; c) HCl, EtOH, 0 °C, 12 h; d) $CHCl_3$, 61 °C, 24-48 h, 85%; e) *t*-BuLi, –35 °C, 5 days; f) $MeSO_3H$, MeOH, 65 °C, 48 h, 64%, 96% ee; g) DMDO (0.06 M), CH_2Cl_2, 0 °C, 4 h, 91:9 d.r.; h) $LiN(SiMe_3)_2$, THF, –78 °C, 10 min, then NH_4Cl, 20 °C, 2 h, 89%, 96% ee; i) Et_3N, $ClSiMe_2CH_2Br$, CH_2Cl_2, 0 °C, 6 h; j) Bu_3SnH, AIBN, PhH, 80 °C, 10 h, 73:27 d.r.; k) KF, $KHCO_3$, H_2O_2 (30%), THF, 20 °C, 12 h, 68%, 97% ee; l) 4 Å MS, $ZnCl_2$, THF, 66 °C, 12 h, 98%, 97% ee.

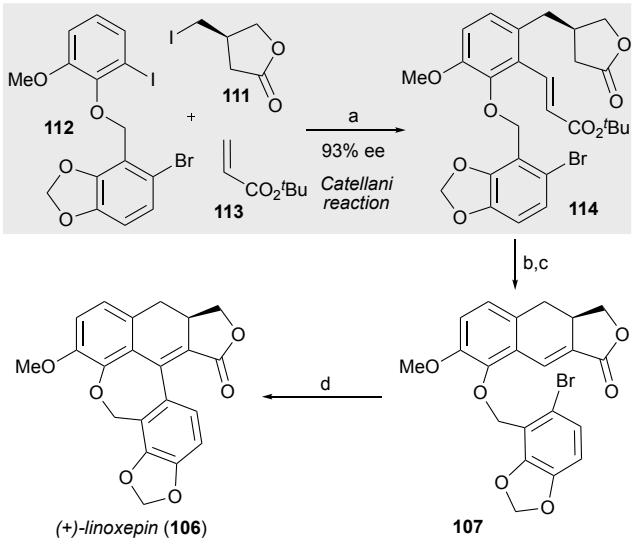


Scheme 26 Lautens synthetic strategy towards (+)-linoxepin.

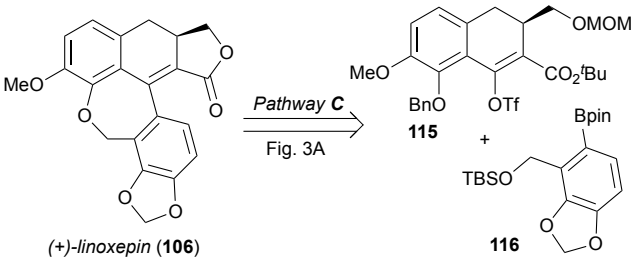


Scheme 27 Synthesis of iodolactone **111**. a) 3-nitrobenzene sulfonyl chloride, Et_3N, CH_2Cl_2, 0 °C, quant.; b) $CH_2(CO_2Me)_2$, CsF, MeCN, 7d, 68%; c) $AlCl_3$ (2 mol%), HCl (2.0 eq.), DME, r.t., quant.; d) pTsOH•H_2O (2.0 eq.), DMSO, 140 °C, 76%; e) NaI, Me(CO)Et, reflux, 98%.

Suzuki–Miyaura reaction to form the C1'–C7' bond (Scheme 29) via pathway ***C*** (Fig. 3A). Kinetic resolution of racemic tetralone *rac*-**117** with chiral urea catalyst **118** afforded **117** in 37% yield with excellent levels of enantioselectivity (99% ee), allowing further processing with triflic anhydride in the presence of sodium hydride to afford vinyl triflate **115** (Scheme 30). The key Suzuki–Miyaura coupling of triflate **115** with aryl borane **116** proceeded smoothly to deliver



Scheme 28 Lauten's total synthesis of (+)-linoxepin. a) $Pd(OAc)_2$ (10 mol%), PPh_3 (22 mol%), Cs_2CO_3 (5.0 eq.), norbornene (5.0 eq.), DMF (sealed tube), 90 °C, 5 h, 89%; b) OsO_4, $NaIO_4$ (3.0 eq.), TEBAC (0.1 eq.), THF, H_2O, 0 °C → r.t., 5 h, 99%; c) $TiCl_4$ (2.2 eq.), Et_3N (5.0 eq.), CH_2Cl_2, –78 °C → –25 °C → r.t., 4 h, 53%, 93% ee; d) $PdCl_2$ (20 mol%), PPh_3 (44 mol%), CsOAc (10.0 eq.), DMF, 75 °C, 4 h, 76%

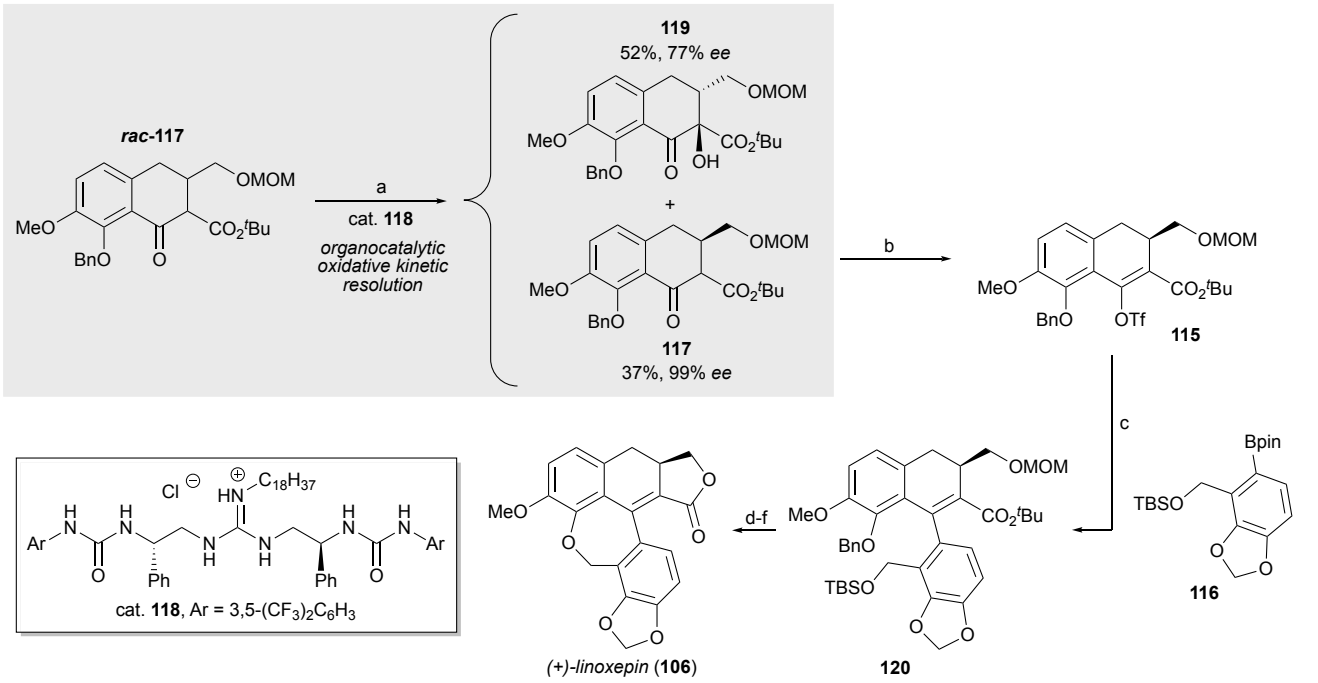


Scheme 29 Nagasawa's synthetic strategy towards (+)-linoxepin.

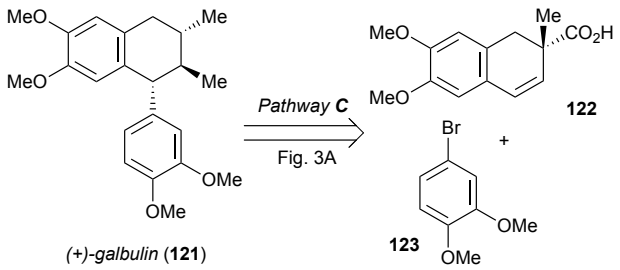
dihydronaphthylene **120**. A subsequent acid-catalyzed deprotection, lactonization, and hydrogenolysis gave a free phenol that engaged in an intramolecular Mitsunobu reaction to complete the total synthesis of (+)-linoxepin (**106**).

3.1.3.4 Galbulin

Clausen and Studer's Synthesis: In 2020, Clausen and Studer synthesized (+)-galbulin (**121**) and several other unnatural lignans.[68] They were inspired by the total syntheses of podophyllotoxin completed by Sherburn and coworkers,[56] and epipodophyllotoxin carried out by Linker and coworkers,[63] each of which involved chiral dihydronaphthalenes as intermediates. Clausen and Studer's synthetic strategy involved the use of pathway ***C*** (Fig. 3A), generating the cyclolignan skeleton from naphthyl and aryl synthons through the formation of the C1'–C7' bond (Scheme 31). Their synthesis commenced with the preparation of naphthalene **125** from commercially available aldehyde **60**. Treatment with conditions described in a patent by Yamada and coworkers[69] was followed by an intramolecular Friedel-Crafts-type reaction. Elimination of ethanol and water gave cyanonaphthalene **125**, which was then converted to naphthalene **126** via treatment with gaseous HCl and subsequent addition of (*S*)-valinol (Scheme 32). Meyers' asymmetric tandem silyl anion addition/alkylation[29] was then used to generate **127**, which gave dihydronaphthalene **122** upon removal of the silyl



Scheme 30 Nagasawa's total synthesis of (+)-linoxepin. a) cat. **118** (5 mol%), CHP (0.75 eq.), K_2CO_3 (1.0 eq.), PhMe, 0 °C, 72 h, **119** = 52%, 77% ee, **117** = 37%, 99% ee; b) Tf_2O (1.2 eq.), NaH (2.0 eq.), Et_2O, 0 °C → r.t., 30 min, 74%; c) $Pd(PPh_3)_4$ (5 mol%), KOH (5.0 eq.), 1,4-dioxane, 60 °C, 1 h, 47%; d) HCl (4M), MeOH, r.t., 3 h; e) H_2, Pd/C (10 wt%), MeOH, r.t., 30 min, 62% over 2 steps; f) DEAD (4.0 eq.), PPh_3 (4.0 eq.), THF, 0 °C → r.t., 30 min, 88%.



Scheme 31 Clausen and Studer's synthetic strategy towards (+)-galbulin.

moiety in 99% ee. They then utilized their stereospecific decarboxylative γ-arylation to yield **128**.[70-74] Next, a diastereoselective hydroboration of **128** with Cl_2BH generated *in situ* and treatment with neopentyl glycol gave an intermediate ester. This then underwent homologation followed by transesterification with pinacol to yield stable pinacol boronic ester **129** with a d.r. of 5:1. The Studer group's protodeboronation protocol[75] successfully yielded a phenylboronate complex, which was then oxidized under photoredox conditions. Trapping of the primary alkyl radial with thiophenol delivered the final product (+)-galbulin (**121**) with a d.r. of 5:1 and a 99% ee. Application of this established strategy enabled the group to synthesize several galbulin analogues in a related manner.

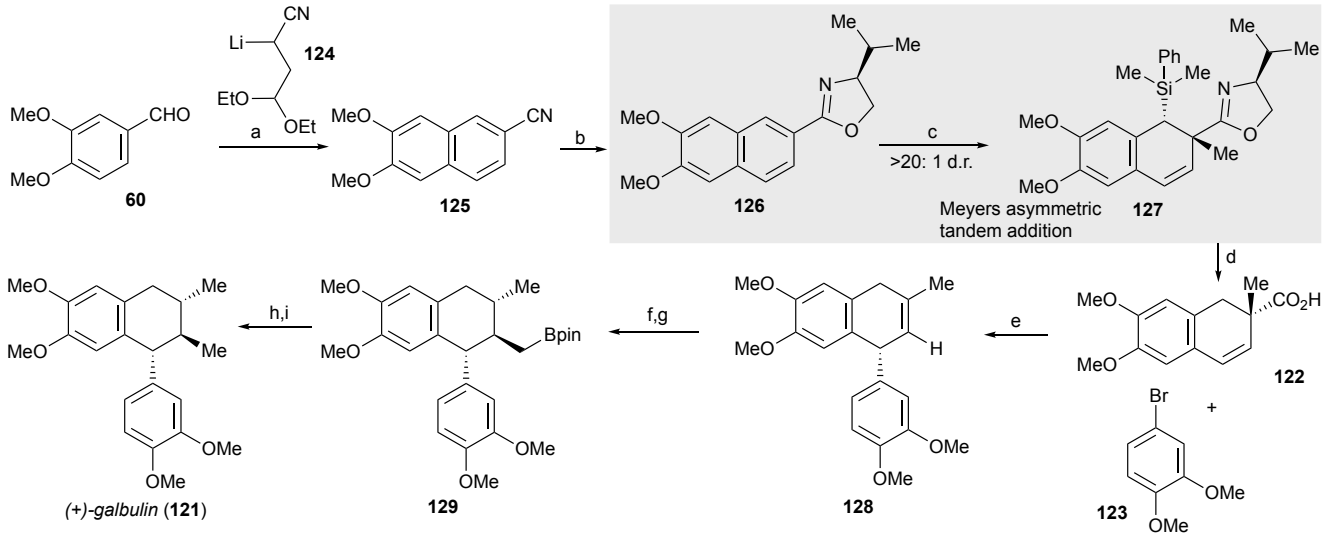
3.1.4 Disconnection D: The 1,4-Diarylbutane Approach

3.1.4.1 Phyltetralin

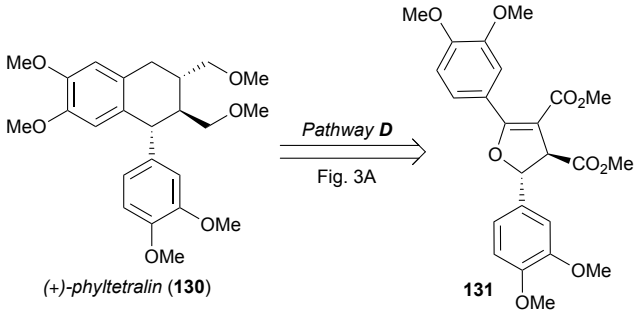
Brun's Synthesis: In 2003, Brun and coworkers published the total synthesis of (+)-phyltetralin (**130**), using a rearrangement of a 2,5-diaryl-2,3-dihydrofuran into a 4-aryltetralone as their key step forming a bond between C2 and C7' (Scheme 33) thus utilizing pathway ***D*** (Fig. 3A).[76] The Brun group had previously reported a diastereoselective Mn(III)-promoted oxidative radical addition of alkyl acetoacetates to *p*-methoxycinnamoyl oxazolidinones to yield *trans*-disubstituted 2,3-dihydrofurans.[77] They expanded this methodology from alkyl acetoacetates to aryl acetoacetate **132** with oxazolidonone **133** to yield the corresponding dihydrofuran, which upon separation of diastereomers and cleavage of the chiral auxiliaries, furnished enantiopure dihydrofuran **131** (Scheme 34). Upon treatment with $SnCl_4$, furan **131** rearranged to 4-aryltetralin **134**, which the authors observed existed in solution as an equilibrium mixture of the enol and *cis*- and *trans*-tetralone forms. Reductive deoxygenation of **134** gave a 70:30 ratio of the *trans*- and *cis*-esters. This ratio was improved to 94:6 by epimerization with sodium methoxide to favor the more stable *trans*-configuration. Final reduction with $LiAlH_4$ and *O*-alkylation completed the total synthesis of (+)-phyltetralin (**130**) in five steps and a 40% overall yield from their dihydrofuran intermediate **131**.

3.1.4.2 Lyoniresinol dimethyl ether

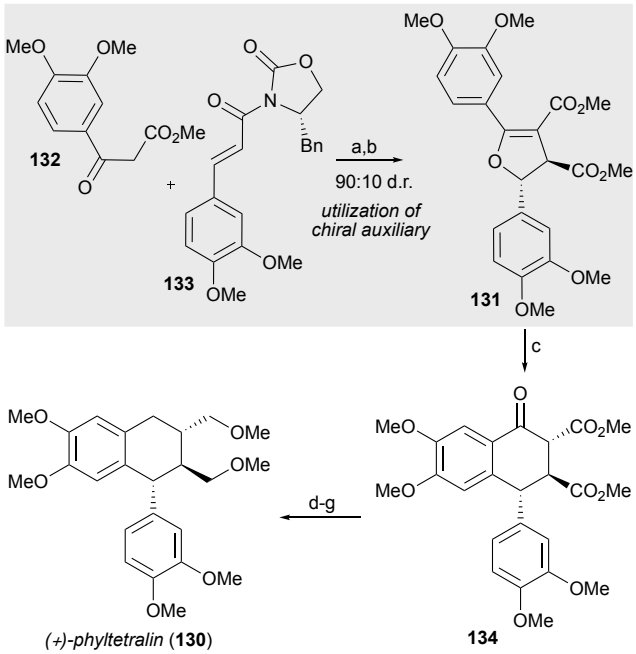
Charlton's Synthesis: In 2001, Charlton and coworkers developed a photochemical method to convert a 2,3-dibenzylidenesuccinate precursor into an optically active dihydronaphthalene, and applied it towards the first asymmetric synthesis of optically pure (+)-lyoniresinol dimethyl ether (**135**) in 2004 (Scheme 35).[78,79] To diacid **137**, (–)-ephedrine **138** was added to prepare the cyclic amide ester **136** as a single rotamer (Scheme 36). The key photochemical cyclization step formed the C2–C7' bond from the 1,4-diarylbutane synthon to give compound **139** through pathway ***D*** (Fig. 3A). Subsequent removal of the chiral auxiliary gave a diacid intermediate **140**, which was converted into the corresponding ethyl ester and



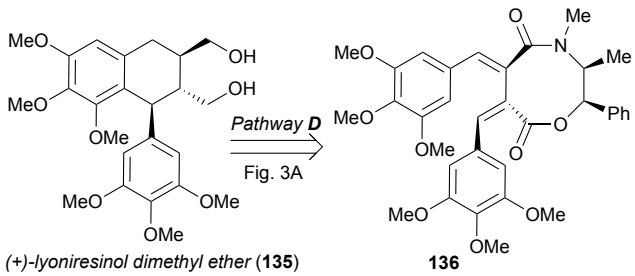
Scheme 32 Clausen and Studer's total synthesis of (+)-galbulin. a) **124** (1.2 eq.), THF, –78 °C → 0 °C, then H_2SO_4 (20%), H_2O/MeOH; b) HCl(g) (bubbled through solution, 2 h), EtOH, 0 °C, then (*S*)-valinol (2.0 eq.), CH_2Cl_2, 40 °C, 24 h; c) $Me_2PhSiLi$ (0.5 M in THF, 3.0 eq.), - 20 °C, 24 h, then Me_2SO_4 (5.0 eq.); d) HCl (3 M in H_2O/dioxane, 1 mL/mmol of **127**); e) **123** (1.2 eq), Cs_2CO_3 (1.3 eq.), $Pd(dba)_2$, (10 mol %), PhMe (0.3 M), 110 °C, 18 h; f) Et_3SiH (3.0 eq.), BCl_3 (1.0 M in CH_2Cl_2, 3.0 eq.), CH_2Cl_2, 0 °C, 3 h, then 2,2-dimethyl-1,3-propanediol (3.0 eq.); g) $BrCH_2I$ (10.0 eq.), *n*-BuLi (1.6 M in hexanes, 8.0 eq.), THF, –78 °C → rt, then NaOH(aq) (0.2 M), pinacol (5.0 eq.); h) PhLi (1.1 eq.), Et_2O, 0 °C → rt, 1 h; i) $Ir(dFCF_3ppy)_2(dtbbpy)PF_6$ (2 mol %), PhSH (1.1 eq.), MeOH/acetone (1:1), blue LED, rt, 18 h.



Scheme 33 Brun's synthetic strategy towards (+)-phyltetralin.



Scheme 34 Brun's total synthesis of (+)-phyltetralin. a) $Mn(OAc)_3$•$2H_2O$ (2.2 eq.), AcOH, 70 °C, 72%, 90:10 d.r.; b) LiBr (5.0 eq.), DBU (2.0 eq.), MeOH, THF, 0 °C, 3 h, 63%; c) $SnCl_4$ (10 eq.), CH_2Cl_2, r.t., 12 h, 93%; d) H_2 (3 bar), Pd/C (10%), AcOH, 80 °C, 8 h, 73%, 7:3 d.r.; e) MeONa (7.0 eq.), MeOH, reflux, 24 h, 81%, 94:6 d.r.; f) $LiAlH_4$ (20 eq.), THF, reflux, 30 min; g) NaH (2.0 eq.), MeI (1.5 eq.), THF, r.t., 6 h, 74% over 2 steps.



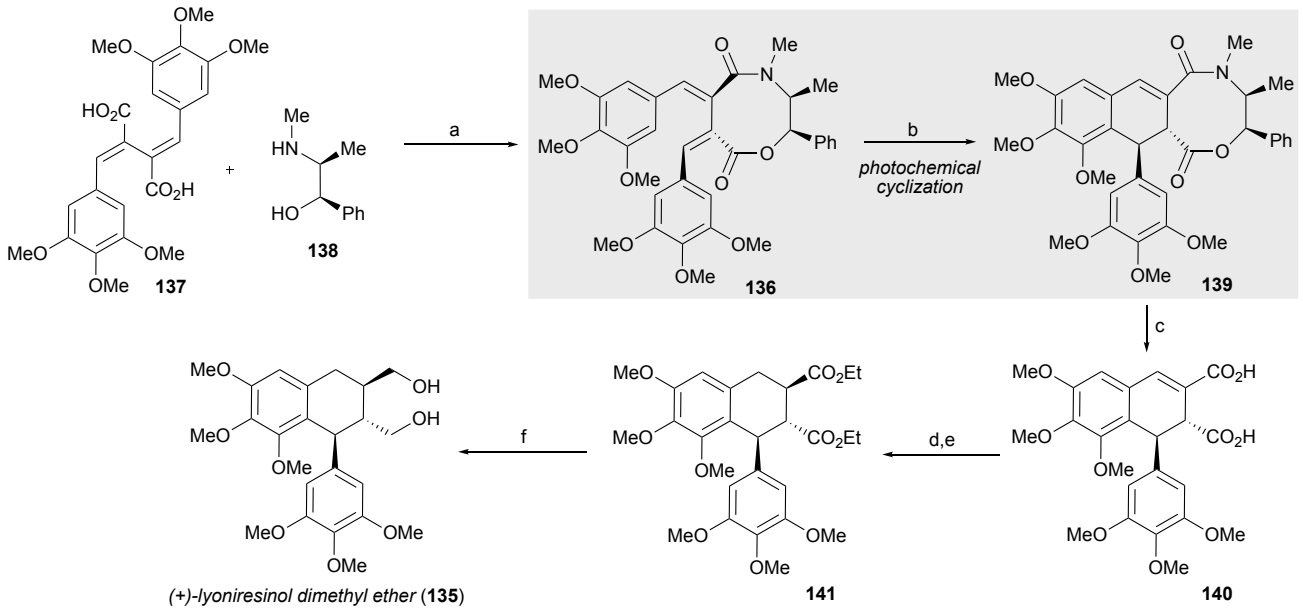
Scheme 35 Charlton's synthetic strategy towards (+)-lyoniresinol dimethyl ether.

then hydrogenated to give diester **141**. Reduction with LAH gave the desired (+)-lyoniresinol dimethyl ether (**135**) (d.r. 80:20) in 5 steps.

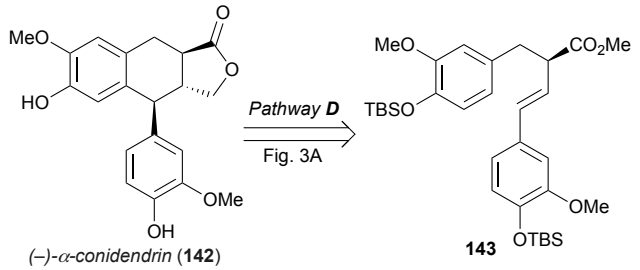
3.1.4.3 α-Conidendrin

Davies' Synthesis: In 2003, Jin and Davies reported the intermolecular C–H insertion to primary benzylic positions with a rhodium carbenoid.[80] This reaction was then used as the key step in the total synthesis of (–)-α-conidendrin (**142**, Scheme 37) via a C2–C7' bond formation through pathway ***D*** (Fig. 3A). As shown in Scheme 38, Rh_2(*S*-DOSP)$_4$ and aryldiazoacetate **145** were used to form the metal carbenoid, which underwent chemoselective C–H insertion into the electron-rich arene **144** with high levels of asymmetric induction to form ester **143** (43% yield, 91% ee). Snider and Jackson had shown previous success forming the cyclolignan core with 1,4-diaryl-1-butenes and para-formaldehyde in a Prins/Friedel–Crafts arylation sequence,[81] which was applied here to install the second methyl substituent and close the cyclohexane ring of diol **146**. Subsequent lactonization with TsOH followed by TBAF deprotection completed the total synthesis of **142**.

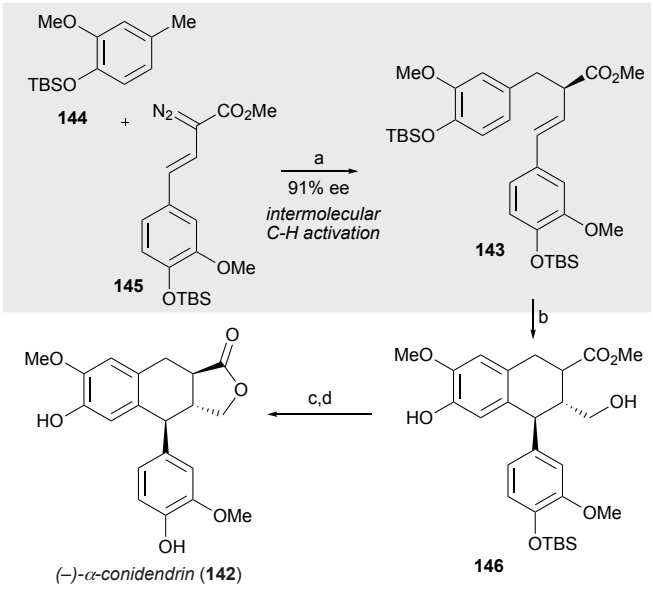
Sherburn's Synthesis: In 2004, Sherburn and coworkers reported the total synthesis of several dibenzylbutyrolactone lignans, such as (–)-



Scheme 36 Charlton's total synthesis of (+)-lyoniresinol dimethyl ether. a) TBTU (1.0 eq.), DIPEA (3.0 eq.), CH_2Cl_2, DMF, 0 °C → r.t., 24 h, 44%; b) *hυ* (254 nm), 2-propanol. 30 min, 26%; c) KOH (3M), MeOH, reflux, 3 h; d) EtOH, H_2SO_4, reflux, 12 h, 54% over 2 steps; e) Pd/C (5%), H_2, MeOH, 12 h, 87%. f) $LiAlH_4$ (12 eq.), THF, r.t., 3 h, no isolated yield reported.



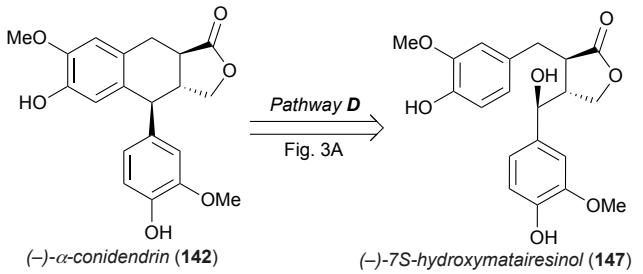
Scheme 37 Davies' synthetic strategy towards (–)-α-conidendrin.



Scheme 38 Davies' total synthesis of (–)-α-conidendrin. a) Rh_2(*S*-DOSP)$_4$ (1 mol%), 2,2-dimethylbutane, reflux, 45 min, 43%, 91% ee; b) $(HCHO)_n$ (6.0 eq.), $MeAlCl_2$•Me_2AlCl (6.0 eq.), CH_2Cl_2, 0 °C, 1 h; c) TsOH (10 mol%), CH_2Cl_2, r.t., 1 h, 58% over 2 steps, 12.5:1 d.r.; d) TBAF (2.3 eq.), THF, r.t., 30 min, 78%

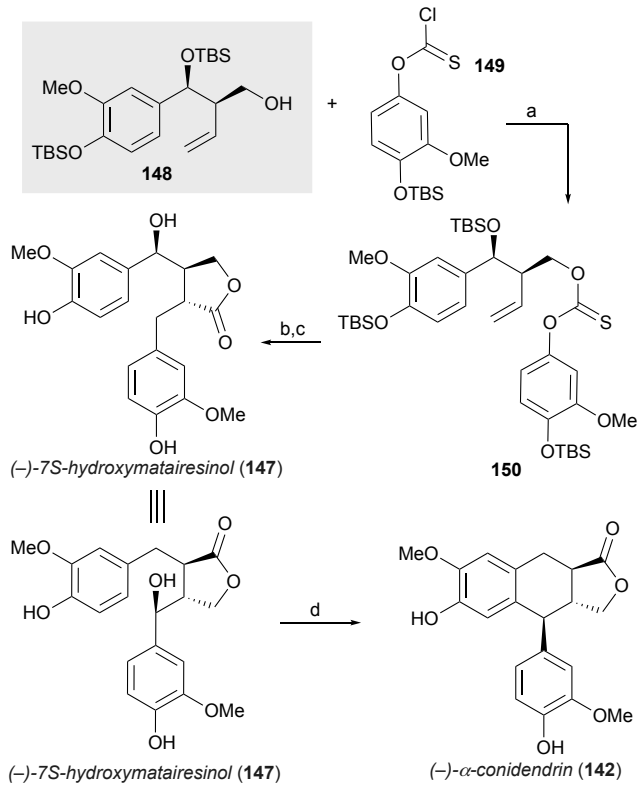
7*S*-hydroxymatairesinol (**147**), which was then converted to (–)-α-conidendrin (**142**) through a key C2–C7′ bond forming reaction (pathway ***D***, Fig. 3A) from a 1,4-diarylbutane synthon (Scheme 39).[82] They used the intramolecular alkene carboxyarylation reaction highlighted in their previously reported syntheses of podophyllotoxin (see Schemes 22, 23 and 40).[56] Homoallylic alcohol **148**, constructed using the same asymmetric Evans *syn*-aldol strategy as in their synthesis of *ent*-**1** (see Scheme 22),[56] was treated with aryl chlorothionoformate **149** to afford thionocarbonate **150**. Intramolecular alkene carboxyarylation of **150** with subsequent deprotection completed the total synthesis of (–)-7*S*-hydroxymatairesinol (**117**), which was converted to (–)-α-conidendrin (**142**) upon treatment with TFA.

Fuchs' Synthesis: In 2013, Fuchs and coworkers developed a catalytic stereoinduction method for the allylation of benzaldehydes using chiral phosphoric acids, most notably (3,3′-bis(2,4,6-tri-isopropylphenyl)-1,1′-binaphthyl - 2,2′- diylhydrogenphosphate (TRIP), and applied it towards the synthesis of (–)-7*S*-hydroxymatairesinol (**147**).[83] They then focused their attention on expanding their this method to include preparation of other natural products, using the same strategy as Sherburn (Scheme 39), involving formation of the C2–C7′ bond via pathway ***D*** (Fig. 3A).[84] This paper discusses the total synthesis of (–)-α-conidendrin (**142**), as well as isostegane, neoisostegane, and (–)-yatein (**15**). Asymmetric TRIP-catalyzed allylation of benzyl protected vanillin **151** with bromolactone **152** yielded β-substituted α-methylenebutyrolactone

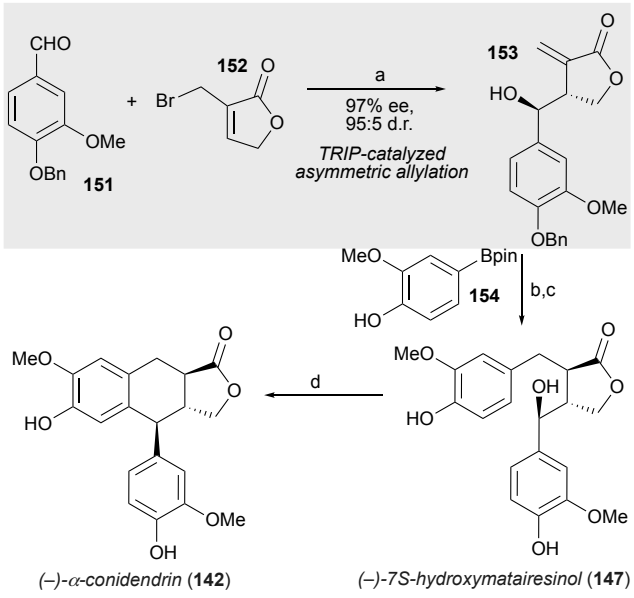


Scheme 39 Sherburn's synthetic strategy towards (–)-α-conidendrin.

153 with nearly perfect diastereo- and enantioselectivity (d.r. >95:5, 97% ee) (Scheme 41). The unsaturated lactone **153** underwent a Rh-catalyzed 1,4-addition of arylboronate **154** to yield the key intermediate **147** (d.r. >95:5). Subsequent Friedel-Crafts alkylation generated the final C2–C7' bond to form (–)-α-conidendrin (**142**) in 4 steps with a 40% overall yield.

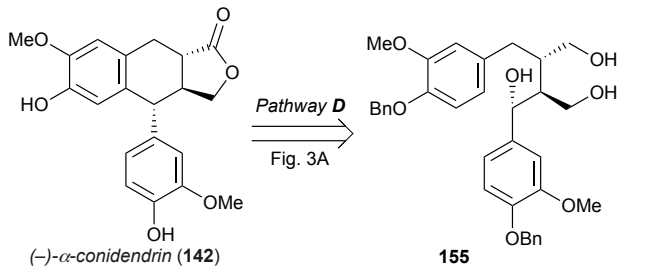


Scheme 40 Sherburn's total synthesis of (–)-α-conidendrin. a) pyridine (2.0 eq.), CH_2Cl_2, 2 h, 81%; b) $(Me_3Si)_3SiH$ (1.1 eq.), AIBN (0.4 eq.), PhH, 80 °C, 6 h, 44%, >95% ee; c) *n*-Bu_4NF (15 eq.), AcOH (15 eq.), THF, 25 °C, 96 h, 90%; d) TFA (3.3 eq.), CH_2Cl_2, 25 °C, 1 h, 100%.

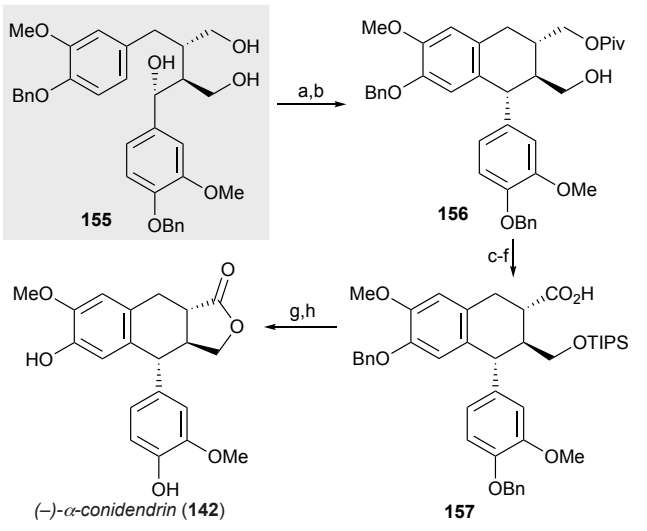


Scheme 41 Fuchs' total synthesis of (–)-α-conidendrin. a) (*R*)-TRIP (20 mol%), Zn (6.3 eq.), NH_4Cl (8.8 eq.), PhMe, *i*-Pr_2O, 4 °C, 16 h, 71%, 97% ee, >95:5 d.r.; b) $[Rh^{I}codCl]_2$ (3.1 mol%), Et_3N (1.0 eq.), dioxane/H_2O 4/1, 70 °C, 3 h, 87%, >95:5 d.r.; c) Pd/C (10 wt%), H_2 (1 atm.), EtOAc, r.t., 16 h, 86%; d) TFA (3.3 eq.), CH_2Cl_2, r.t., 24 h, 76%.

Yamauchi's Synthesis: Yamauchi and coworkers developed an interest in (–)-α-conidendrin (**142**) due to studies on its bioactivity,[85-87] and in 2020 published work covering the syntheses of all eight stereoisomers of the natural product.[88] Their synthetic strategy involved use of retrosynthetic pathway ***D*** (Figure 3A), generating the key C2–C7' bond from a 1,4-diarylbutane synthon (Scheme 42). Triol **155** was obtained from the corresponding lactone,[89] which was prepared from L-glutamic acid[90] via γ-butyrolactone.[91] Upon protection with pivaloyl chloride, the pivaloyl ester product underwent intramolecular Friedel-Crafts reaction with 10-camphorsulfonic acid (CSA) giving **156** (Scheme 43). Some undesired pivaloyl ester was also formed, but it could be converted back into starting material via hydrolysis. Primary alcohol **156** was TIPS-protected, and reductive cleavage of the pivaloyl ester freed up the other alcohol, which subsequently underwent two oxidations affording carboxylic acid **157**. Desilylation with *n*-Bu_4NF, dehydration with *p*-TsOH and hydrogenolysis of the benzyl ether formed the final product (–)-α-conidendrin (**142**) with >99% ee. The other stereoisomers of



Scheme 42 Yamauchi's synthetic strategy towards (–)-α-conidendrin.

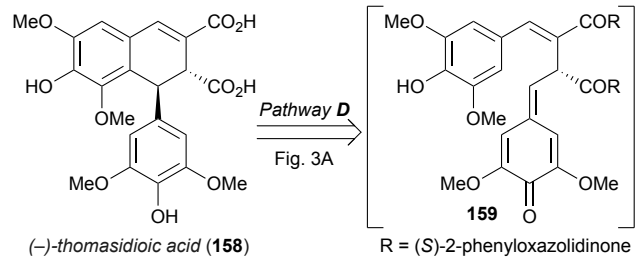


Scheme 43 Yamauchi's total synthesis of (–)-α-conidendrin. a) PivCl (1.3 eq.), pyridine (2.6 eq.), CH_2Cl_2, r.t., 24 h, 31%; b) CSA (6.8 mol%), CH_2Cl_2, r.t., 19 h, 55%; c) 2,6-lutidine (2.5 eq.), TIPSOTf (1.2 eq.), CH_2Cl_2, r.t., 1 h, 91%; d) DIBAL-H (3.0 eq.), PhMe, – 10 °C, 1 h, 88%; e) PCC (2.3 eq.), MS 4Å, CH_2Cl_2, r.t., 22 h, 62%; f) 2-methyl-2-butene (4.4 eq.), $NaH_2PO_4 \bullet 2H_2O$ (1.0 eq.), $NaClO_2$ (2.7 eq.), *t*-BuOH, H_2O, 0 °C → r.t., 4 h, 80%; g) *n*-Bu_4NF (1.3 eq.), THF, r.t., 19 h, then *p*-TsOH (12 mol%), PhMe, 60 °C, 24 h, 93%; h) 5% Pd/C (300% by wt.), H_2, EtOAc, r.t., 5 h, 76%.

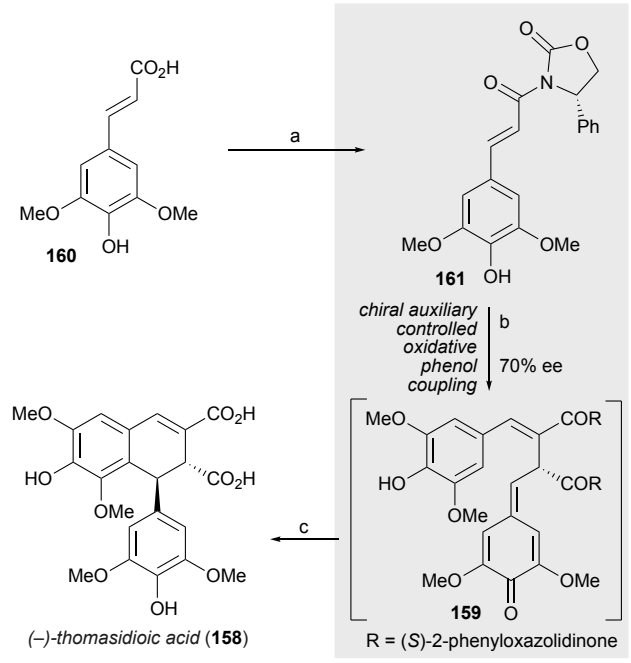
conidendrin were achieved with high enantioselectivity by either changing the enantiopure starting material **155**, or by epimerizing C8' stereocenter on alcohol **156** in three steps.

3.1.4.4 Thomasidioic acid

Orlandi's Synthesis: Thomasidioic acid (**158**) was isolated in 1969 from *Ulmus thomasii* as a racemic mixture.[92] In 1997, Charlton and Lee showed that racemic thomasidioic acid could be prepared through air oxidation of sinapic acid in a basic solution, which raised the question of whether or not thomasidioic acid was actually a natural product.[93] In 2008, Orlandi and coworkers employed an enzymatic oxidative coupling strategy to complete the first enantioselective total synthesis of (–)-thomasidioic acid (**158**) in just three steps from commercially available sinapic acid (**160**).[94] Their synthetic strategy involved the formation of the C2–C7' bond from a 1,4-diarylbutane synthon (Scheme 44) thus utilizing pathway ***D*** (Fig. 3A). Sinapic acid (**160**) was first coupled with (*S*)-(+)-4-phenyl-2-oxazolidinone **28** to form sinapamide **161** (Scheme 45). This was subsequently treated with horseradish peroxidase (HRP) in the presence of hydrogen peroxide to yield *trans*-dihydronaphthalene



Scheme 44 Orlandi's synthetic strategy towards (–)-thomasidioic acid.

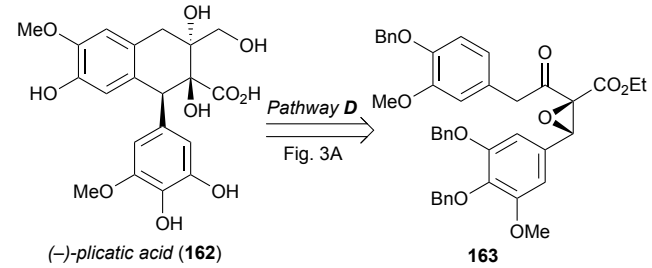


Scheme 45 Orlandi's total synthesis of (–)-thomasidioic acid. a) CMPI (1.0 eq.), **28** (1.0 eq.), Et_3N (1.3 eq.), CH_2Cl_2, r.t., 5 d, 40%; b) H_2O_2 (0.5 eq.), Horseradish Peroxidase enzyme, phosphate/citric acid buffer (pH 3.5), 1,4-dioxane, 0 °C, 4 h, 40%, 70% de; c) H_2O_2, LiOH (17 eq.), THF, r.t., 18 h, 60%.

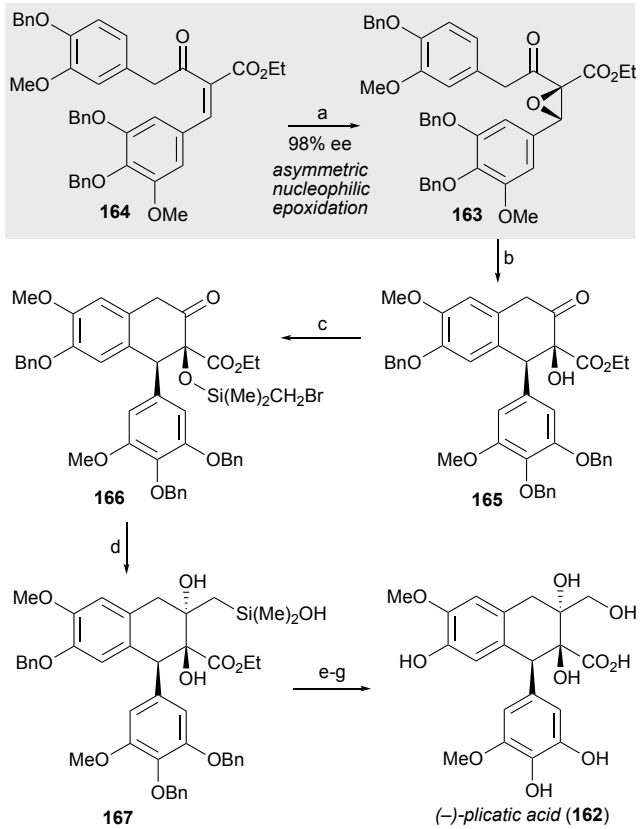
159 in 70% diastereomeric excess. Hydrolysis of the chiral auxiliary was achieved with lithium peroxide to complete the total synthesis of (–)-thomasidioic acid (**158**).

3.1.4.5 Plicatic acid

Deng's Synthesis: In 2009, Deng and coworkers published the first enantioselective total synthesis of (–)-plicatic acid (**162**) using an asymmetric epoxidation.[95] Their synthetic strategy involved generating the C2–C7' bond through pathway ***D*** from a 1,4-diarylbutane synthon (Scheme 46). The authors first developed a method for the enantioselective and diastereoselective epoxidation of electron-deficient tri-substituted olefins, and then applied that method in their total synthesis. Trisubstituted olefin **164** was prepared through the Knoevenagel condensation, and then used to generate epoxide **163** (Scheme 47). Epoxide **163** was then treated



Scheme 46 Deng's synthetic strategy towards (–)-plicatic acid.

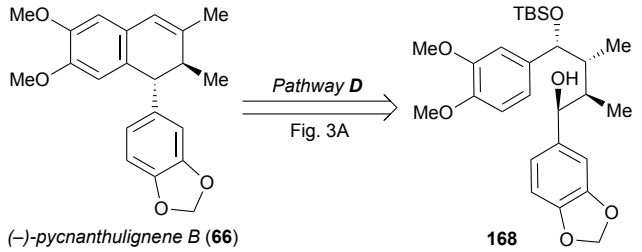


Scheme 47 Deng's total synthesis of (–)-plicatic acid. a) (*S,S*)-TADOOH (1.1 eq.), LiOH (0.1 eq.), THF, 0 °C → r.t., 18 h, 83%, 98% ee; b) TfOH (0.04 eq.), CH_2Cl_2, 0 °C → r.t., 15 min, 70%, 4:1 d.r., >98% ee; c) $ClSi(Me)_2CH_2Br$ (3.2 eq.), imidazole (3.0 eq.), DMF, r.t., 1 h, 75% (94% brsm); d) SmI_2 (3.5 eq.), NiI_2 (0.1 eq.), THF, 0 °C, 1 h, 58%; e) H_2O_2 (18 eq.), $NaHCO_3$ (6.4 eq.), MeOH, THF, r.t., 12 h, 87% (90% brsm); f) *n*-PrSNa (1.3 eq.), DMF, 50 °C, 24 h, 97%; g) H_2, Pd/C (15%), MeOH, r.t., 4 h, then Dowex-50, 72%.

with substoichiometric amounts of TfOH to promote the Friedel–Crafts reaction yielding **165** with good selectivity (d.r. 4:1). Silylation of the free alcohol in **165** led to **166**, which upon treatment with SmI_2 and NiI_2 underwent an intramolecular Barbier reaction to yield hydroxysilane **167**. Fleming–Tamao–Kumada oxidation of **167** furnished the triol, which was subsequently treated with sodium propanethiolate to cleave the ester. Global benzyl deprotection followed by cationic exchange completed the total synthesis of (–)-plicatic acid (**162**) in 12 steps and 14% overall yield.

3.1.4.6 Dihydronaphthalene Lignans

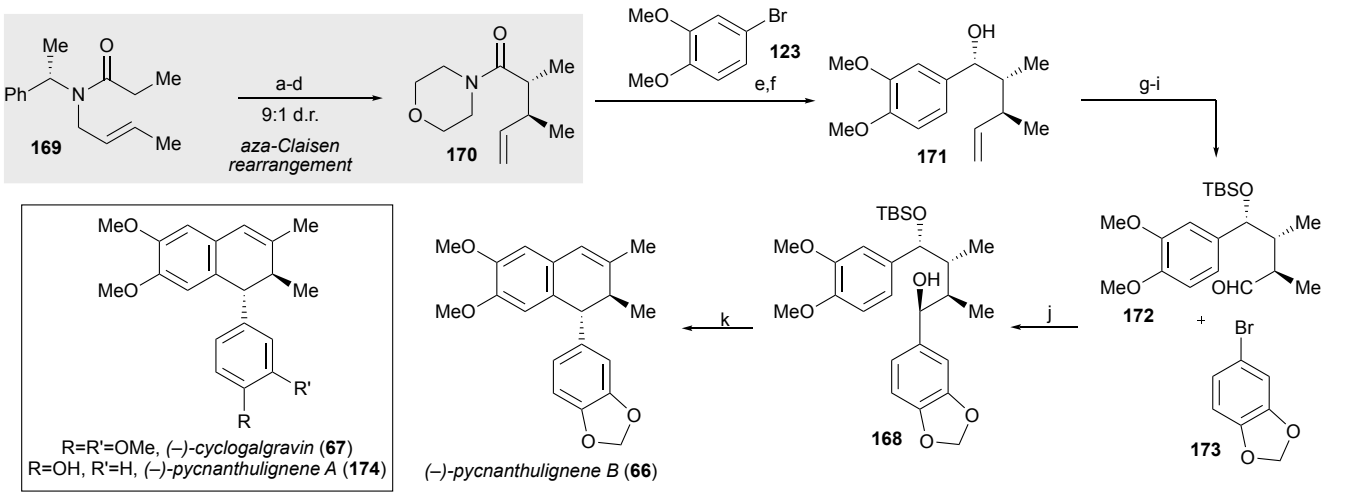
Barker's Synthesis: In 2011, Barker and coworkers reported the total synthesis of five lignan natural products.[96] The synthesis of three cyclolignans, (–)-cyclogalgravin (**67**),[36] (–)-pycnanthulignene A (**174**),[37] and (–)-pycnanthulignene B (**66**)[37] was included in this report. Their synthetic strategy involved the formation of the key C2–C7' bond from a 1,4-diarylbutane synthon (Scheme 48) via pathway ***D*** (Fig. 3A). Known chiral amide **169** underwent an aza-Claisen rearrangement to afford the corresponding dimethyl amide, which was then transformed to the free acid through an iodolactonization/reductive ring-opening sequence (Scheme 49). Coupling of the free acid with morpholine afforded amide **170** with excellent selectivity (d.r. 9:1). Addition of lithiated 4-bromoveratrole **123** followed by sodium borohydride reduction of the resulting ketone furnished alcohol **171** as a single diastereomer. Alcohol **171** served as a common intermediate for the synthesis of the three cyclolignans, as well as a tetrahydrofuran lignan (+)-galbelgin. For the cyclolignan syntheses, alcohol **171** was protected as the TBDMS ether before the olefin was oxidatively cleaved in a two-step procedure to yield aldehyde **172**. The addition of lithiated 1-bromo-3,4-methylenedioxybenzene **173** to **172** afforded a single diastereomer of alcohol **168**, which upon treatment with mesyl chloride, rearranged to yield the natural product (–)-pycnanthulignene B (**66**). Aldehyde **172** served as the common intermediate for the three cyclolignans; simple replacement of the aryl lithium reagent changed the resulting cyclolignan natural product. Treatment of **172** with lithiated 4-bromoveratrole, followed by mesyl chloride produced (–)-cyclogalgravin (**67**), while lithiated 1-bromo-4-(methoxymethoxy)benzene produced pycnanthulignene A (**174**) upon deprotection. In a subsequent publication Barker and Davidson reported that the product of the mesyl chloride promoted rearrangement was highly dependent of the substitution pattern of the aromatic rings of alcohols such as **171**.[97] In some cases, the rearrangement of 1,4-diarylbutane-1,4-diols led to the formation of 4,4-diarylbutanals, rather than 4-aryltetralins.



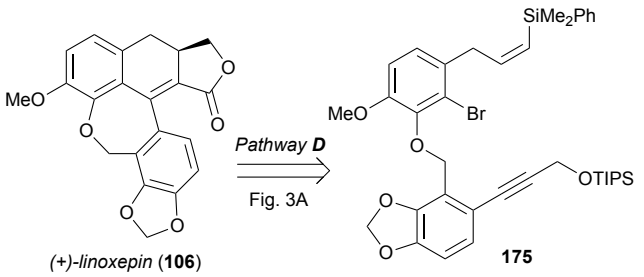
Scheme 48 Barker's synthetic strategy for dihydronaphthalene lignans.

3.1.4.7 Linoxepin

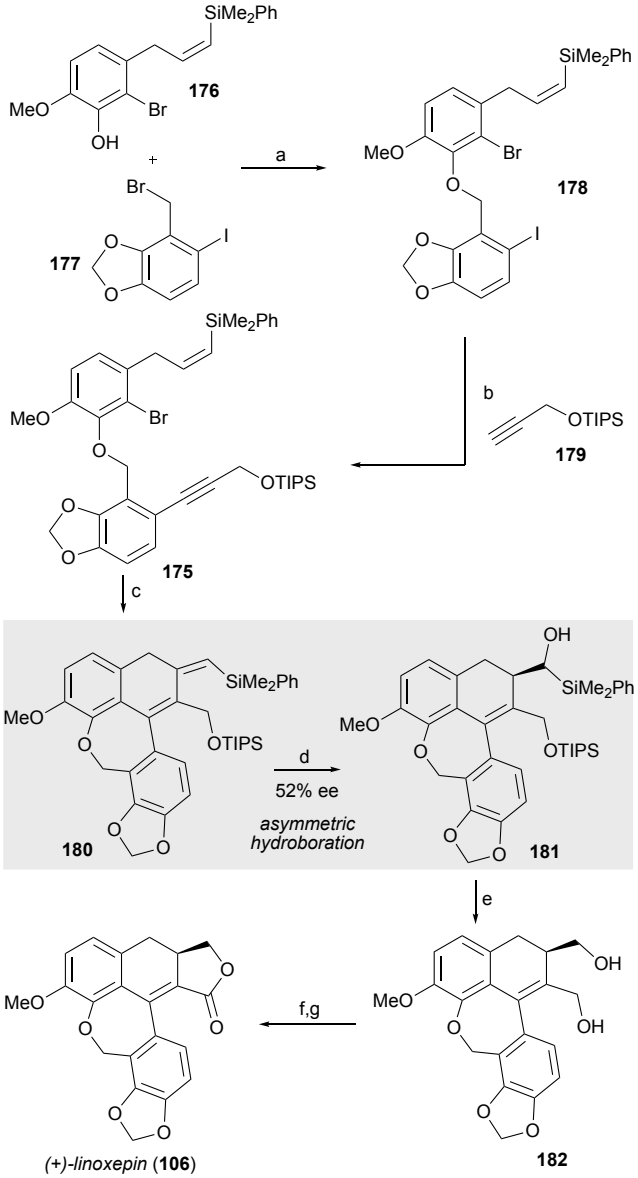
Tietze's Synthesis: Tietze and coworkers reported the first total synthesis of racemic linoxepin in 2013[98] and subsequently reported a related enantioselective synthesis of (+)-linoxepin (**106**) in 2014.[99] The Tietze group, like the Lautens lab, chose to tether the aryl rings by constructing the C3–C2' linkage at the beginning of their synthesis, but the key disconnection in this case is between the C2–C7' bond (Scheme 50). This strategy most closely aligns with pathway ***D*** from Figure 3A, although the final ring is closed during the formation of the key bond. Alkylation of phenol **176** with aryl bromide **177** led to ether **178**, which was subsequently coupled to protected propargyl alcohol **179** through a Sonogashira reaction (Scheme 51). A palladium-catalyzed domino reaction of alkyne **175** formed vinyl silane **180**. The lone stereocenter of the natural product was introduced through asymmetric hydroboration of alkene **180** with Brown's borane, furnishing dihydronaphthalene **181** with



Scheme 49 Barker's total synthesis of three dihydronapthalene lignans. a) *n*-BuLi (1.4 eq.), HMDS (1.4 eq.), PhMe, 140 °C, 24 h, 72%, 9:1 d.r.; b) I_2 (2.2 eq.), H_2O, THF, r.t., 20 h; c) Zn (8.7 eq.), AcOH, 60 °C, 18 h, 74% over 2 steps; d) morpholine (1.1 eq.), DCC (1.1 eq.), DMAP (25 mol%), 73%; e) *t*-BuLi (2.0 eq.), THF, –78 °C, 81%; f) $NaBH_4$ (4.0 eq.), MeOH, –78 °C → r.t., 92%; g) TBSOTf (1.2 eq.), 2,6-lutidine (4.0 eq.), CH_2Cl_2, 72%; h) OsO_4 (1 mol%), NMO (3 eq.), *t*-BuOH, H2O, r.t., 94%; i) $NaIO_4$ (1.2 eq.), MeOH, H_2O, 90%; j) *t*-BuLi (2.0eq.), THF, –78 °C, 59%; k) MsCl (1.3 eq.), Et_3N (1.6 eq.), CH_2Cl_2, 1 h, 95%.



Scheme 50 Tietze's synthetic strategy towards (+)-linoxepin.



Scheme 51 Tietze's total synthesis of (+)-linoxepin. a) K_2CO_3 (2.2 eq.), MeCN, 80 °C, 3.5 h, 99%; b) $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), *n*-Bu_4NOAc (3.0 eq.), 1,4-dioxane, 60 °C, 30 min, 94%; c) $Pd(OAc)_2$ (10 mol%), DavePhos (50 mol%), Ag_2CO_3 (1.4 eq.), DMAP (1.0 eq.), PhMe, 110 °C, 45 min, 96%; d) (–)-$(ipc)BH_2$ (4.0 eq.), THF, 0 °C → r.t., 16 h, then H_2O_2 (30%), NaOH (2 M), 0 °C → r.t., 1 h, 77%; e) TBAF (2.5 eq.), THF, 0 °C, 1 h, 89%, 52% ee; f) MnO_2 (10 eq.), CH_2Cl_2, r.t., 2.5 h; g) I_2 (1.5 eq.), K_2CO_3 (3.5 eq.), *t*-BuOH, 50 °C, 4.5 h, 75% over 2 steps.

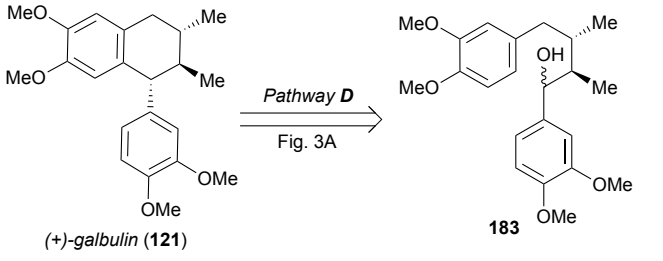
moderate enantioselectivity (52% ee). Deprotection of **181** with TBAF afforded the diol **182**, which was then treated with MnO_2 to selectively oxidize the allylic alcohol. Oxidation of the aldehyde with I_2 in the presence of K_2CO_3 led to lactone formation and completed the total synthesis of (+)-linoxepin (**106**) in eleven steps with a total isolated yield of 27%.

3.1.4.8 Galbulin

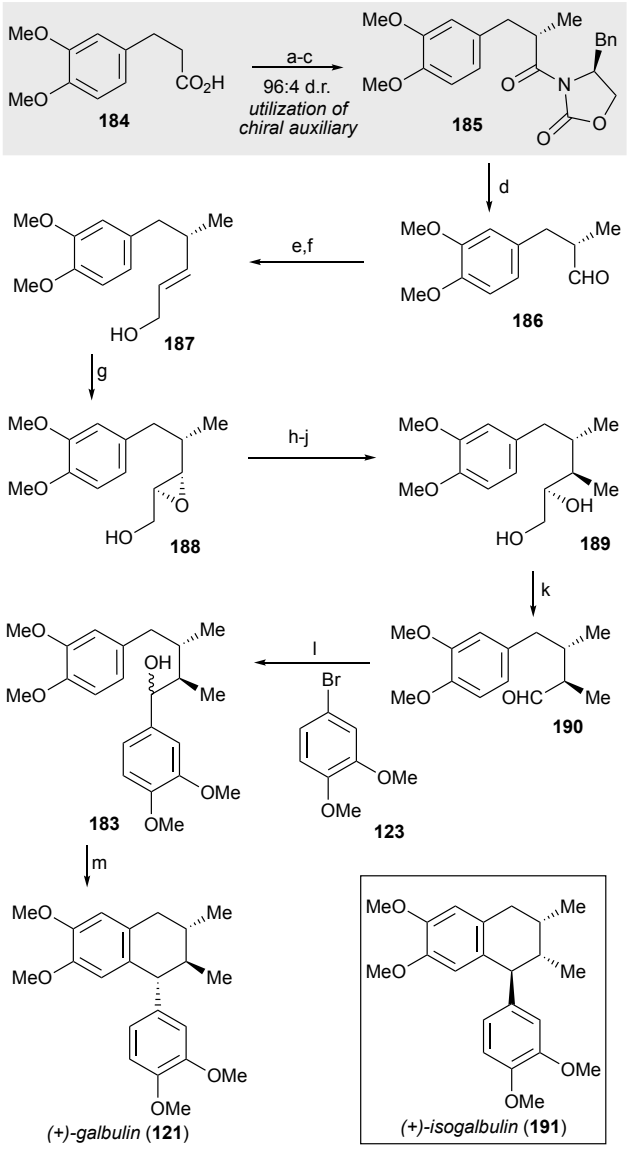
Xie's Synthesis: In 2014, Xie and coworkers reported enantioselective syntheses of (+)-galbulin (**121**) and (+)-isogalbulin (**191**) utilizing a key intramolecular Friedel-Crafts cyclization to form the final C2–C7' bond (Scheme 52) via pathway ***D*** as shown in Figure 3A.[100] Oxazolidinone **185** was prepared from an Evans asymmetric alkylation (Scheme 53). Reduction of this oxazolidinone **185** generated aldehyde **186**, which was converted to allylic alcohol **187** by a Wittig olefination and subsequent reduction. Sharpless asymmetric epoxidation of allylic alcohol **187** induced by (+)-DIPT afforded epoxide **188** (d.r. 92:8). The hydroxyl group of the epoxide compound **188** was benzyl protected allowing for application of modified Pfalt's conditions[101] (as determined by the Flippin group)[102] for reductive epoxide opening to yield diol **189** after protecting group removal. Following oxidative cleavage to give aldehyde **190** and addition of aryllithium **123**, the key intermediate alcohol **183** was prepared, which underwent a smooth Friedel-Crafts cyclization to give (+)-galbulin (**121**) in 10 steps with an overall 13% yield. The same method was used to prepare (+)-isogalbulin (**191**) with a total yield of 12.3%, using (–)-DIPT in the Sharpless asymmetric epoxidation step.

3.1.4.9 Isodehydroxypodophyllotoxin

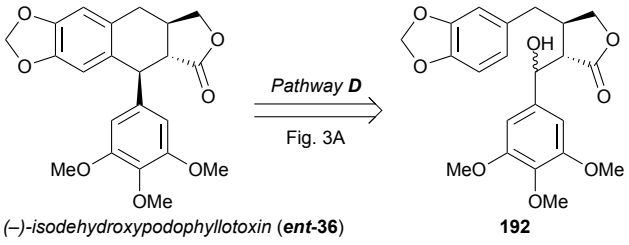
Ceroni and Cozzi's Synthesis: (–)-Isodehydroxypodophyllotoxin (***ent*-36**) was isolated in 1967 by Kuhn and von Wartburg.[103] In 2015, the Ceroni and Cozzi groups demonstrated a straightforward approach towards this molecule via a key stereoselective organocatalytic photoredox transformation using an iron(II) tri(bipyridine) complex, whose photophysical properties had been previously elucidated.[104-108] They showed that $[Fe(bpy)_3]Br_2$ and visible light could successfully replace $[Ru(bpy)_3]^{2+}$ and other common photosynthesizers, advancing the area of photocatalysis to include earth-abundant and the more economical first-row transition metals.[109, 110] Their strategy involved the key formation of the C2–C7' bond through pathway ***D*** (Fig. 3A) from a 1,4-diarylbutane synthon (Scheme 54). Under visible light irradiation, substoichiometric amounts of $[Fe(bpy)_3]Br_2$ in the presence of MacMillan organocatalyst **195** were found to readily promote stereoselective alkylation of aldehydes with α-bromo carbonyl compounds. To highlight the utility of this methodology, Ceroni and Cozzi developed a concise synthesis of (–)-



Scheme 52 Xie's synthetic strategy towards (+)-galbulin.



Scheme 53 Xie's total synthesis of (+)-galbulin. a) *t*-BuCOCl (1.1 eq.), Et_3N (1.2 eq.), THF, −78 °C, 1 h; b) (*S*)-oxazolidinone (1.1 eq.), LDA (1.2 eq.) THF, −78 °C → r.t., 24 h, 91%, >99% ee; c) LDA (1.1 eq.), THF, −78 °C, 30 min, then MeI (4.5 eq.), −78 °C → r.t., 2.5 h, 69%, 92% de; d) DIBAL-H, CH_2Cl_2, −78 °C, 80%; e) $Ph_3P{=}CHCO_2Me$, PhMe, CH_2Cl_2, 50 °C, 89%; f) DIBAL-H, CH_2Cl_2, 0 °C, 87%; g) $Ti(O\text{-}iPr)_4$ (40 mol%), (+)-DIPT (0.5 eq.), TBHP (2.0 eq.), 4Å MS, CH_2Cl_2, −78 °C → −23 °C, 7 h, 85%, 92:8 d.r.; h) NaH, Bu_4NI, THF, BnBr, 92%; i) Me_3Al (2.2 eq.), *n*-BuLi (1.1 eq.), PhMe, −78 °C → r.t., 6 h, 76%; j) H_2, $Pd(OH)_2$, MeOH, AcOH, r.t., 2 h, 93%; k) $NaIO_4$, THF, H_2O, r.t., 72%; l) *n*-BuLi, THF, −78 °C, 73%; m) HF-pyridine, MeCN, r.t., 72%.

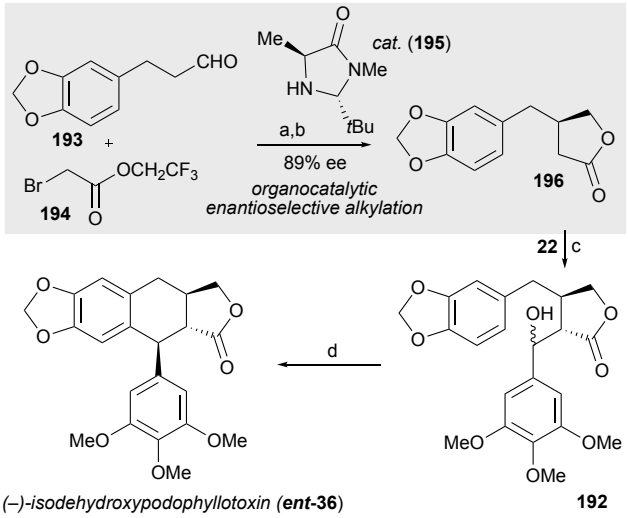


Scheme 54 Ceroni and Cozzi's strategy towards (–)-isodehyroxypodophyllotoxin.

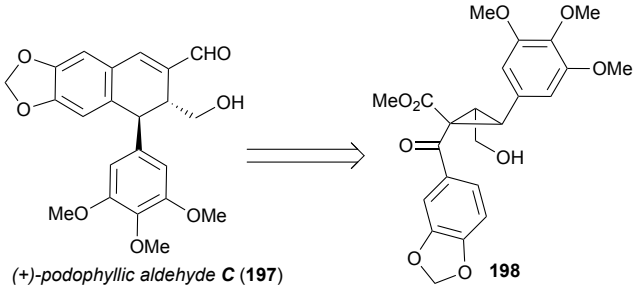
isodehydroxypodophyllotoxin (***ent*-36**) (Scheme 55). Hydrocinnamic aldehyde **193** was alkylated with bromo ester **194**, and subsequent reduction of the resulting aldehyde led to formation of the corresponding lactone **196** with good selectivity (89% ee). Deprotonation of lactone **196** with LiHMDS in the presence of 3,4,5-trimethoxybenzaldehyde (**22**) yielded alcohol **192**, which underwent dehydration upon protonation and displacement by the electron-rich 1,3-benzodioxole to yield (–)-isodehydroxypodophyllotoxin (***ent*-36**) with 91% ee in four steps from aldehyde **193**.

3.1.4.10 Podophyllic Aldehydes

Nishii's Synthesis: While podophyllotoxin has been found to possess a number of biological activities, efforts have been made to prepare analogues that are not only more potent, but also less toxic and more selective.[111] The Castro group has taken a special interest in podophyllic aldehydes and has worked towards developing new derivatives and analyzing their biological activities.[111-114] Podophyllic aldehydes A, B, and C, as prepared and analyzed by the Castro lab, have been found to possess antineoplastic cytotoxicity and apoptosis-inducing capabilities; thus, Nishii and coworkers were very interested in developing new methods to synthesize these compounds.[115] The Nishii group's strategy for the synthesis of (+)-podophyllic aldehydes in 2015 involved the unique use of a chiral transfer ring expansion from a 1,4-diarylbutane synthon to form the C2–C7' bond via pathway ***D*** (Fig. 3A) in the cyclolignan skeleton of the podophyllic aldehydes (Scheme 56).[115] To begin the synthesis, α-



Scheme 55 Ceroni and Cozzi's synthesis of (–)-isodehydroxypodophyllotoxin. a) *hν* (23W CFL), $[Fe(bpy)_3]Br_2$ (2.5 mol%), 2,6-lutidine (2.0 eq.), DMF, 25 °C, 16 h; b) $NaBH_4$ (4.0 eq.), CH_2Cl_2, MeOH, 0 °C, 2 h, 72% over 2 steps, 89% ee; c) LiHMDS (4.0 eq.), THF, −10 °C → 0 °C; d) TFA, CH_2Cl_2, 71% over 2 steps

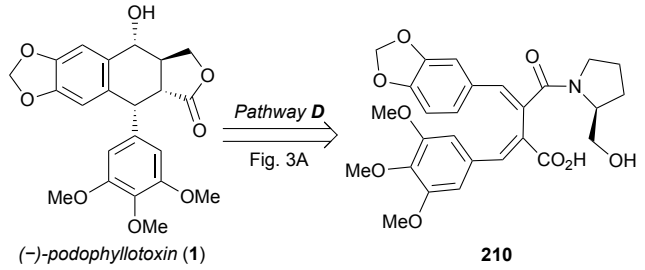


Scheme 56 Nishii's strategy towards (+)-podophyllic aldehydes.

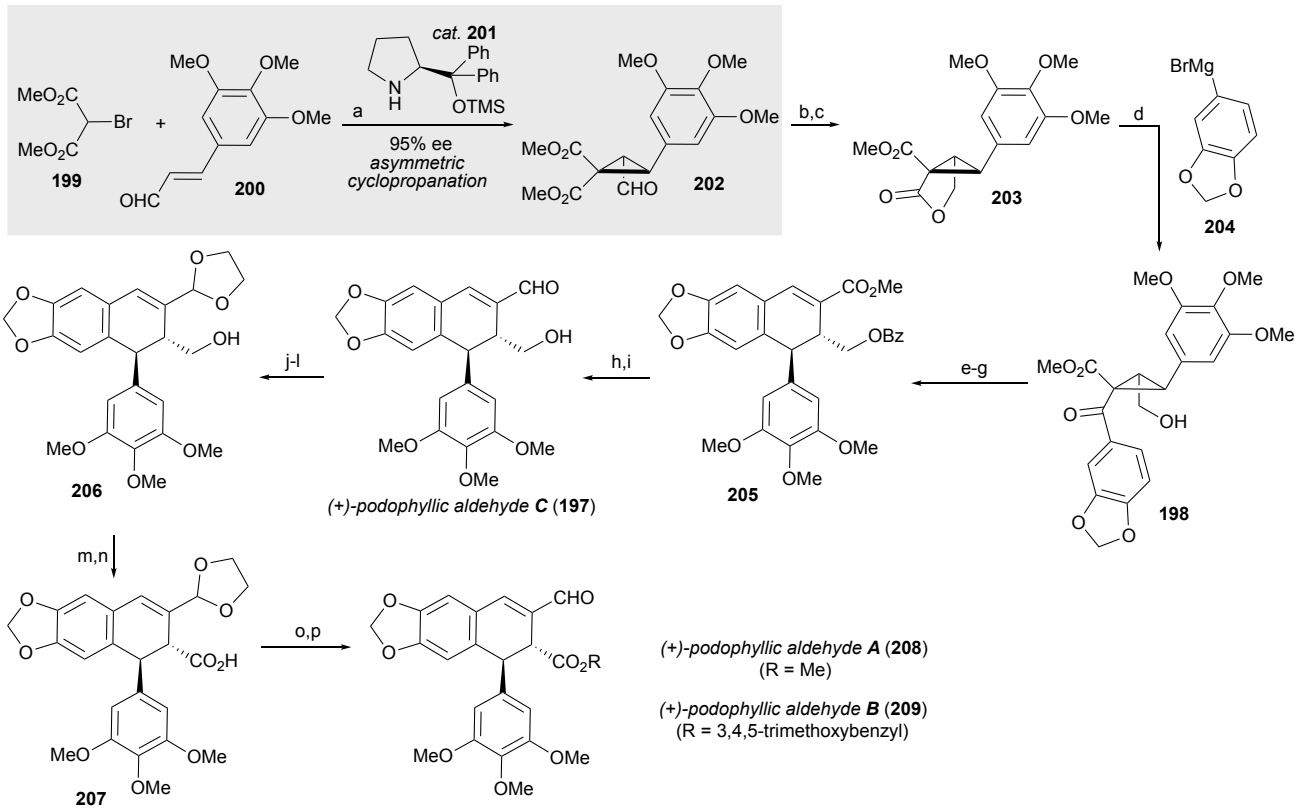
bromomalonate **199** and aldehyde **200** were treated with organocatalyst **201** to produce the asymmetric cyclopropanation product **202** (Scheme 57). Reduction of diester **202** followed by lactonization produced γ-lactone **203** with excellent selectivity (95% ee). Addition of Grignard reagent **204** afforded alcohol **198**, which was then benzyl-protected prior to reduction with $NaBH_4$ to give hydroxyester **205** (d.r. 6:1, 95% ee). Both diastereomers were converted to the same enantiomer of dihydronaphthalene **205** following the Lewis acid-mediated chiral transfer ring expansion to form the central six-membered ring through the key C2–C7′ bond formation (95% ee). Reduction gave a diol and subsequent oxidation produced (+)-podophyllic aldehyde C (**197**) with excellent selectivity (95% ee). Benzoyl protection generated an aldehyde that was acetal-protected, and hydrolysis gave alcohol **206**, which underwent Swern oxidation and subsequent Pinnick oxidation to generate carboxylic acid **207**. When methylated or benzylated, then subsequently deprotected, (+)-podophyllic aldehyde A (**208**) (95% ee) or (+)-podophyllic aldehyde B (**209**) (95% ee) respectively, were formed. This synthetic method can also be utilized to prepare (–)-podophyllic aldehydes by simply using the opposite enantiomer catalyst in the cyclopropanation step. Thus (+)-podophyllic aldehyde A (**208**), (+)-podophyllic aldehyde B (**209**), and (+)-podophyllic aldehyde C (**197**) were synthesized with overall yields of 30%, 26%, and 43% respectively, in 16, 16, and 8 total steps, respectively.

3.1.4.11 Podophyllotoxin

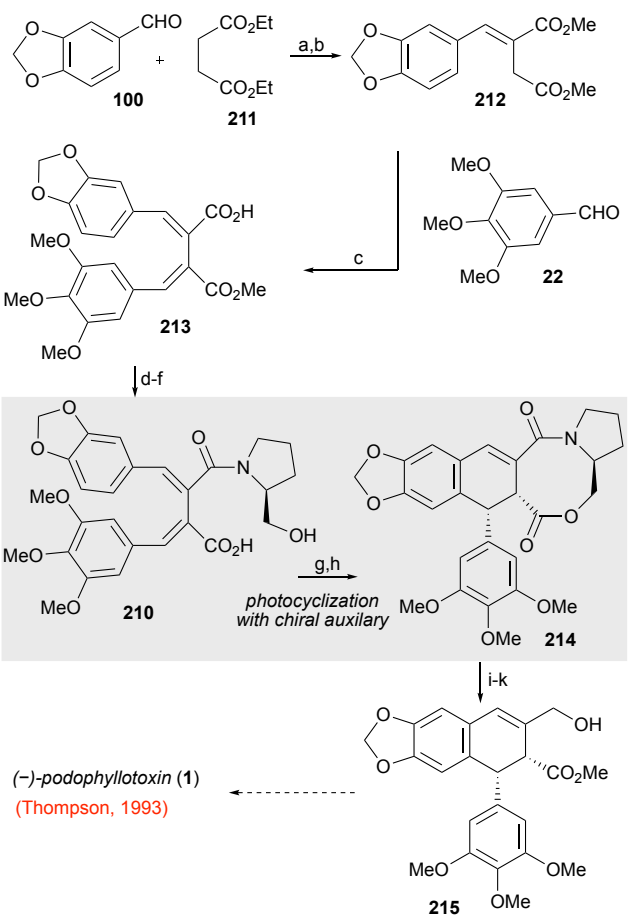
Czarnocki's Synthesis: Czarnocki and coworkers previously developed photocyclization strategies that produced compounds with similar features to podophyllotoxin (**1**)[116] and adapted their methods for its formal total synthesis in 2016.[117] The key step in their synthetic strategy was the photocyclization of a chiral amide ester to generate the C2–C7′ bond from a 1,4-diarylbutane synthon (Scheme 58, also refer to similar scheme 35). Reacting piperonal **100** with diethyl succinate **211** gave an α,β-unsaturated ester intermediate, which went through Fischer esterification with methanol following hydrolysis to give diester **212** (Scheme 59). Condensation with **22** yielded compound **213**, to which a chiral auxiliary was introduced, and the product subsequently hydrolyzed to give acid **210**. Macrolactonization was completed with DCC/DMAP and then the



Scheme 58 Czarnocki's synthetic strategy towards (–)-podophyllotoxin.



Scheme 57 Nishii's total synthesis of (+)-podophyllic aldehydes. a) 2,6-lutidine (1.1 eq.), CH_2Cl_2, 0 °C, 92 h, 91%, 95% ee; b) $NaBH_4$ (1.4 eq.), THF, MeOH, r.t., 15 min; c) *p*-TsOH•H_2O (1 mol%), $CHCl_3$, 45 °C, 2 h, 86% over 2 steps, 95% ee; d) THF, 0 °C, 15 min, 94%; e) BzCl (1.3 eq.), Et_3N (1.3 eq.), CH_2Cl_2, r.t., 1.5 h, 95%; f) $NaBH_4$ (7.4 eq.), THF, MeOH, 0 °C → r.t., 40 min, 70%, 6:1 d.r.; g) BF_3•OEt_2 (1.1 eq.), EDC, reflux, 7 min, 93%, 95% ee; h) DIBAL-H (1.02 M), CH_2Cl_2, –78 °C, 30 min, 96%; i) MnO_2 (58 eq.), CH_2Cl_2, r.t., 5.5 h, 97%; j) BzCl (1.4 eq.), Et_3N (1.4 eq.), CH_2Cl_2, 0 °C → r.t., 1 h, 98%; k) *p*-TsOH•H_2O (15 mol%), ethylene glycol (30 eq.), PhH, r.t., 5.5 h; l) $NaBH_4$ (0.3 eq.), THF, EtOH, 0 °C, 15 min, then KOH (5.0 eq.), MeOH, 0 °C → r.t., 50 min, 93% over 2 steps; m) Et_3N (6.0 eq.), $(COCl)_2$ (2.0 eq.), DMSO (3.0 eq.), CH_2Cl_2, –78 °C, 40 min, 92%; n) $NaClO_2$ (1.1 eq.), NaH_2PO_4•$2H_2O$ (1.1 eq.), 2-methyl-2-butene (20 eq.), *t*-BuOH, H_2O, 0 °C, 55 min; o) **208** = RI (1.9 eq.), **209** = RBr (1.5 eq.), K_2CO_3 (1.3 eq.), DMF, 0 °C → r.t., 1 h; p) HCl (4 M), THF, 0 °C → r.t., 1 h, **208** = 85% over 3 steps, 95% ee, **209** = 72% over 3 steps, 95% ee.

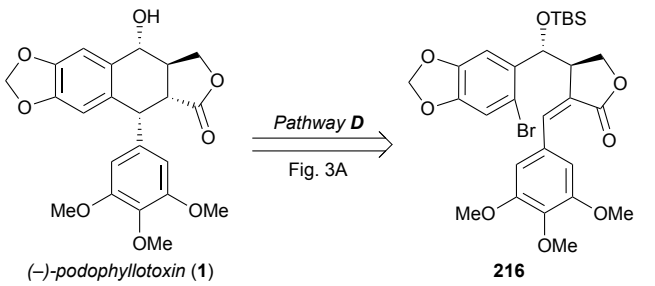


Scheme 59 Czarnocki's formal synthesis of (–)-podophyllotoxin. a) *t*-BuOK (6.7 eq.), PhMe, r.t., 1.5 h, then H_2O, EtOH, 60 °C, 1 h; b) MeOH, AcCl, 0 °C → 80 °C, 12 h, 66% over 2 steps; c) *t*-BuOK (1.1 eq.), PhMe, r.t., 1.5 h, 76%. d) $(COCl)_2$ (2.0 eq.), CH_2Cl_2, 0 °C → r.t., 2 h; e) L-prolinol (1.2 eq.), Et_3N (3.0 eq.), CH_2Cl_2, r.t., 1 h, 99% over 2 steps; f) K_2CO_3 (5.0 eq.), MeOH, H_2O, r.t. → 80 °C, 3 h, 99%; g) DCC (1.5 eq.), DMAP (1.1 eq.), CH_2Cl_2, r.t., 5 h, 74%; h) MeOH, TFA (0.01M), *hυ*, in-flow (0.7 ml/min), 61%; i) MeOH, HCl, 40 °C, 45 min, 94%; j) $Cp_2Zr(H)Cl$ (2.0 eq.), THF, r.t., 10 min, 67%; k) $NaBH_4$ (1.5 eq.), MeOH, 0 °C → r.t., 30 min, 90%.

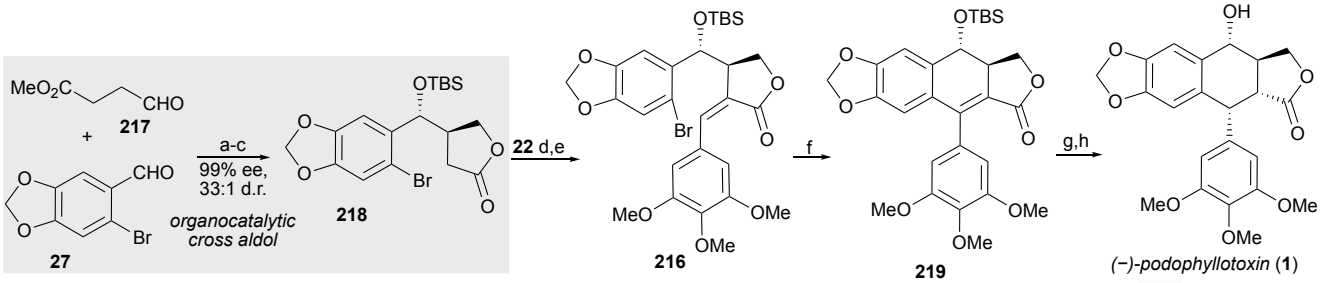
key photocyclization reaction was conducted to form the C2–C7' bond and deliver dihydronaphthylene **214**. Methanolysis opened the 8-membered ring and the resulting compound was reduced with Schwartz's reagent to form an aldehyde; further reduction gave alcohol **215**, an intermediate in the Thompson synthesis of podophyllotoxin.[118, 119] Thus, the formal synthesis of **1** was completed in 9 steps from **100** with a 13% overall yield.

Hajra's Synthesis: While there had previously been many elegant asymmetric syntheses of (–)-podophyllotoxin (**1**) via chiral pool, chiral auxiliary, or resolution strategies, Hajra and coworkers developed the first catalytic enantioselective total synthesis of **1** and several natural analogues, as well as a formal synthesis of ***ent*-1**.[120] Their retrosynthetic strategy employed a common backbone that could be readily diversified into different aryltetralin lignans, and was prepared through pathway ***D*** (Fig. 3A) involving a key C2–C7' disconnection (Scheme 60). The organocatalytic crossed aldol reaction of 6-bromopiperonal **27** and excess donor aldehyde **217** afforded trans-lactone **218** with excellent selectivity (d.r. 33:1) (Scheme 61). A second aldol reaction was completed to produce the major diastereomer *Z*-benzylidine lactone **216**, which was subsequently utilized in an intramolecular Heck cyclization to yield enantiopure dihydronaphthalene **219**. Stereocontrolled reduction afforded the natural product **1** in five steps with a 27% total yield. Adjusting the reduction conditions also provided both (–)-picropodophyllin (**2**) and (+)-isopicropodophyllin, the latter of which could be oxidized with PDC to yield (+)-isopicropodophyllone, an intermediate in the synthesis of ***ent*-1**.[56]

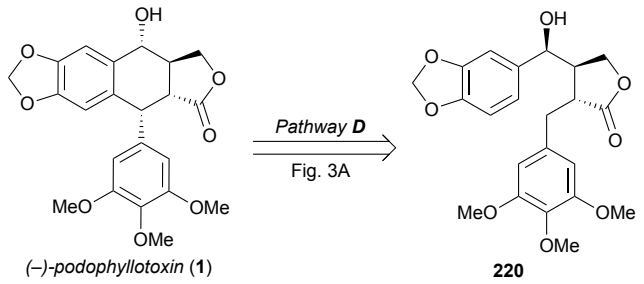
Fuchs' Synthesis: In 2019, Fuchs and coworkers designed a chemoenzymatic route towards the synthesis of (–)-podophyllotoxin (**1**) using 2-oxoglutarate-dependent dioxygenases (2-ODDs) to form the key C2–C7' bond through pathway ***D*** (Fig. 3A) from a 1,4-diarylbutane synthon (Scheme 62).[14] Bromolactone **152** and piperonal **100** were coupled using a zinc source to give alcohol **221**, which underwent another coupling reaction with aryl boronate **222** to give alcohol ***rac*-220** as a racemic mixture (Scheme 63). 2-ODD-PH selectively reacted with the C7 *S*-diastereomer (**220**) through a biocatalytic kinetic resolution process. The key C2–C7' bond was formed to give (–)-epipodophyllotoxin (**38**) (d.r. >95:5). Oxidation with DMP and reaction with L-selectide gave (–)-podophyllotoxin (**1**) with an overall yield of 17% over 5 steps (d.r. >95:5).



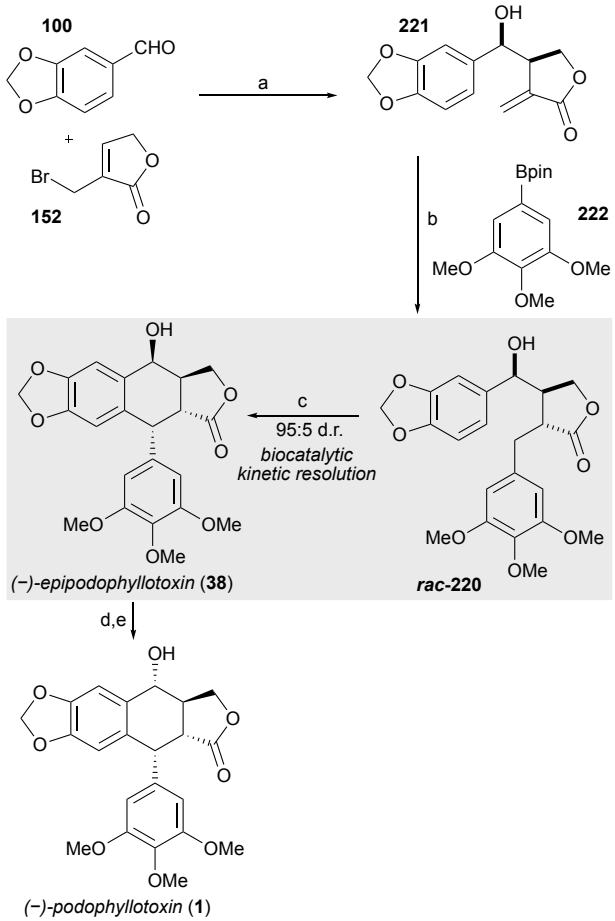
Scheme 60 Hajra's synthetic strategy towards (–)-podophyllotoxin.



Scheme 61 Hajra's total synthesis of (–)-podophyllotoxin. a) L-proline (0.3 eq.), DMF, 4 °C, 24 h, then $NaBH_4$ (3.0 eq.), MeOH, 0 °C, 2 h; b) PPTS (0.1 eq.), PhMe, 65 °C, 8 h, 75% over 2 steps, 33:1 d.r.; c) 2,6-lutidine (2.0 eq.), TBSOTf (1.5 eq.), THF, 0 °C, 12 h, 94%, 10:1 d.r.; d) LiHMDS (1.2 eq.), THF, –78 °C, 6 h; e) MsCl (2.0 eq.), Et_3N (5.0 eq.), CH_2Cl_2, 0 °C → r.t., 4 h, then DBU (3.0 eq.), 0 °C → r.t., 12 h, 84% over 2 steps, 10:1 d.r.; f) Pd_2dba_3 (5 mol%), P(*o*-tol)$_3$ (0.1 eq.), DIPEA (2.0 eq.), DMF, 80 °C, 12 h, 84%; g) Pd/C (20% by wt.), HCO_2Na (0.3 eq.), H_2O, *n*-pentanol, 40 °C, 12 h; h) TBAF (2.0 eq.), AcOH (2.0 eq.), THF, 0 °C, 2 h, 54% over 2 steps.

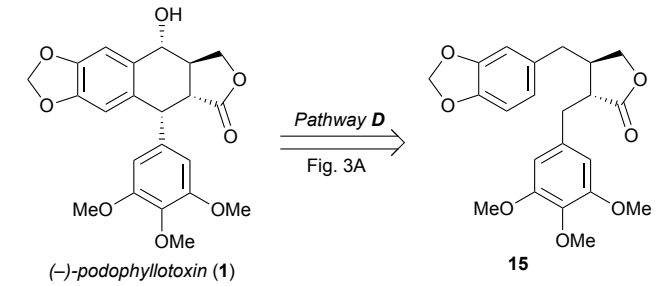


Scheme 62 Fuch's synthetic strategy towards (–)-podophyllotoxin.

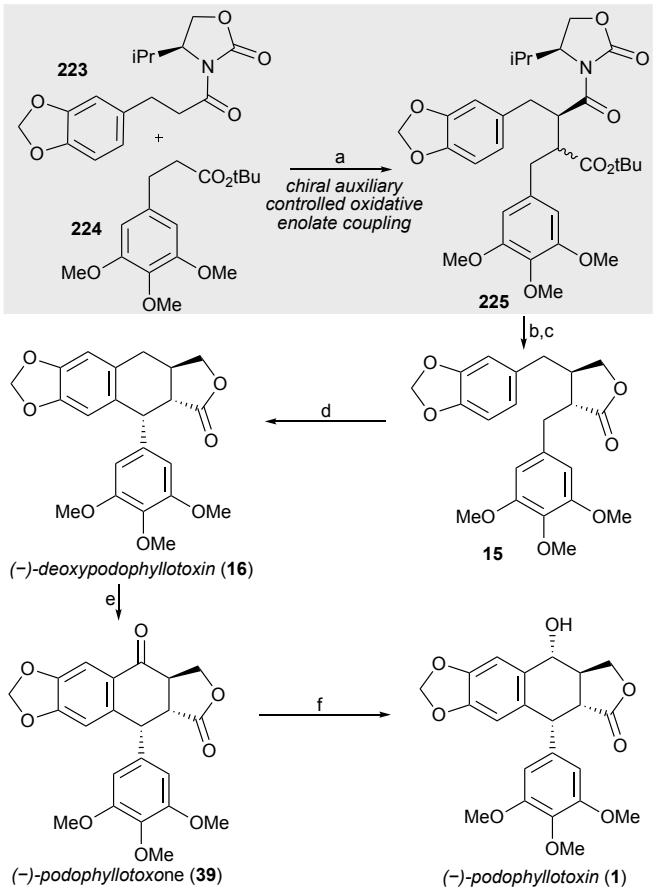


Scheme 63 Fuch's chemoenzymatic synthesis of (–)-podophyllotoxin. a) Zn (2.0 eq.), NH_4Cl (4.0 eq.), PhMe, DME, r.t., 12 h, 99%; b) $[(Rh(cod)Cl]_2$ (3 mol%), Et_3N (1.0 eq.), 1,4-dioxane, H_2O, 70 °C, 3 h, 87%; c) 2-ODD-PH, Fe^{II}, Na ascorbate, 2-oxoglutarate, CFE (44 v%), TRIS buffer (pH = 7.4), DMSO, 18 °C, 18 h, 39%, >95:5 d.r.; d) DMP (1.5 eq.), pyridine (2 eq.), CH_2Cl_2, 0 °C, 16 h, 76%, >95:5 d.r.; e) L-selectride (1.3 eq.), THF, –78 °C, 2 h, 70%, >95:5 d.r.

Renata's Synthesis: In contrast to Fuchs' chemoenzymatic synthesis, Renata and coworkers developed an asymmetric, chemoenzymatic synthesis for the formation of (–)-podophyllotoxin (**1**) that established absolute stereochemistry earlier in the synthesis, thus eliminating the need for a kinetic resolution process to generate the enantioenriched cyclic product.[8] The Renata group's synthesis in 2019 takes advantage of a nonheme dioxygenase (2-ODD-PH) that biocatalytically produces the C2–C7′ bond to form the final ring in the natural product from a 1,4-diarylbutane synthon (Scheme 64), utilizing pathway ***D*** as shown in Figure 3A. They then applied their strategy towards the synthesis of (–)-podophyllotoxin (**1**) and its natural analogues. Utilizing the oxidative enolate coupling methods developed in the Baran lab,[121] oxazolidinone **223** and ester **224** were coupled to produce a mixture of diastereomers (Scheme 65). This proved inconsequential, as subsequent reduction of the dicarbonyl product **225** with $LiBH_4$ produced the pivotal dibenzylbutyrolactone precursor (–)-yatein (**15**) as a single diastereomer due to absolute stereoconfiguration at C8. 2-ODD-PH was prepared for the chemoenzymatic cyclization by using clarified lysate of *E. coli* expressing N-His_6-tagged 2-ODD-PH with co-expression of the chaperones GroEL and GroES to enhance solubility. When used in the reaction, the aryltetralin backbone was produced to generate



Scheme 64 Renata's synthetic strategy towards (–)-podophyllotoxin.

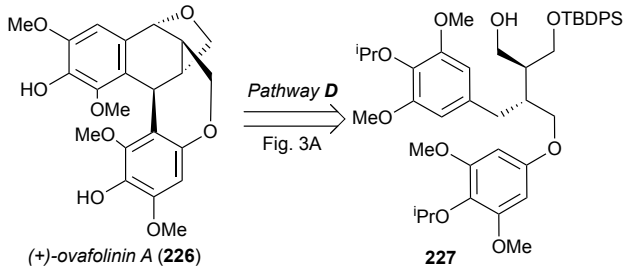


Scheme 65 Renata's chemoenzymatic synthesis of (–)-podophyllotoxin. a) LDA (2.5 eq.), Cu(II)-2-ethylhexanoate (2.5 eq.), THF, –78 °C → 0 °C, 1.5 h; b) $LiBH_4$ (4.0 eq.), THF, 0 °C, 40 min; c) DBU (5 eq.), PhMe, 110 °C, 24 h, 51% over 3 steps; d) 2-OOD-PH lysate, O_2, α-ketoglutaric acid (2.5 eq.), L-ascorbic acid (0.5 eq), $FeSO_4 \bullet 7H_2O$ (0.1 eq.), 50 mM kPi (pH=8.0), DMSO, r.t., 20 h, 95%; e) CrO_3 (5.0 eq.), 3,5-DMP (5 eq.), CH_2Cl_2, 0 °C, 2 h, 62%; f) L-selectride (1.2 eq.), THF, –78 °C, 15 min, 93%.

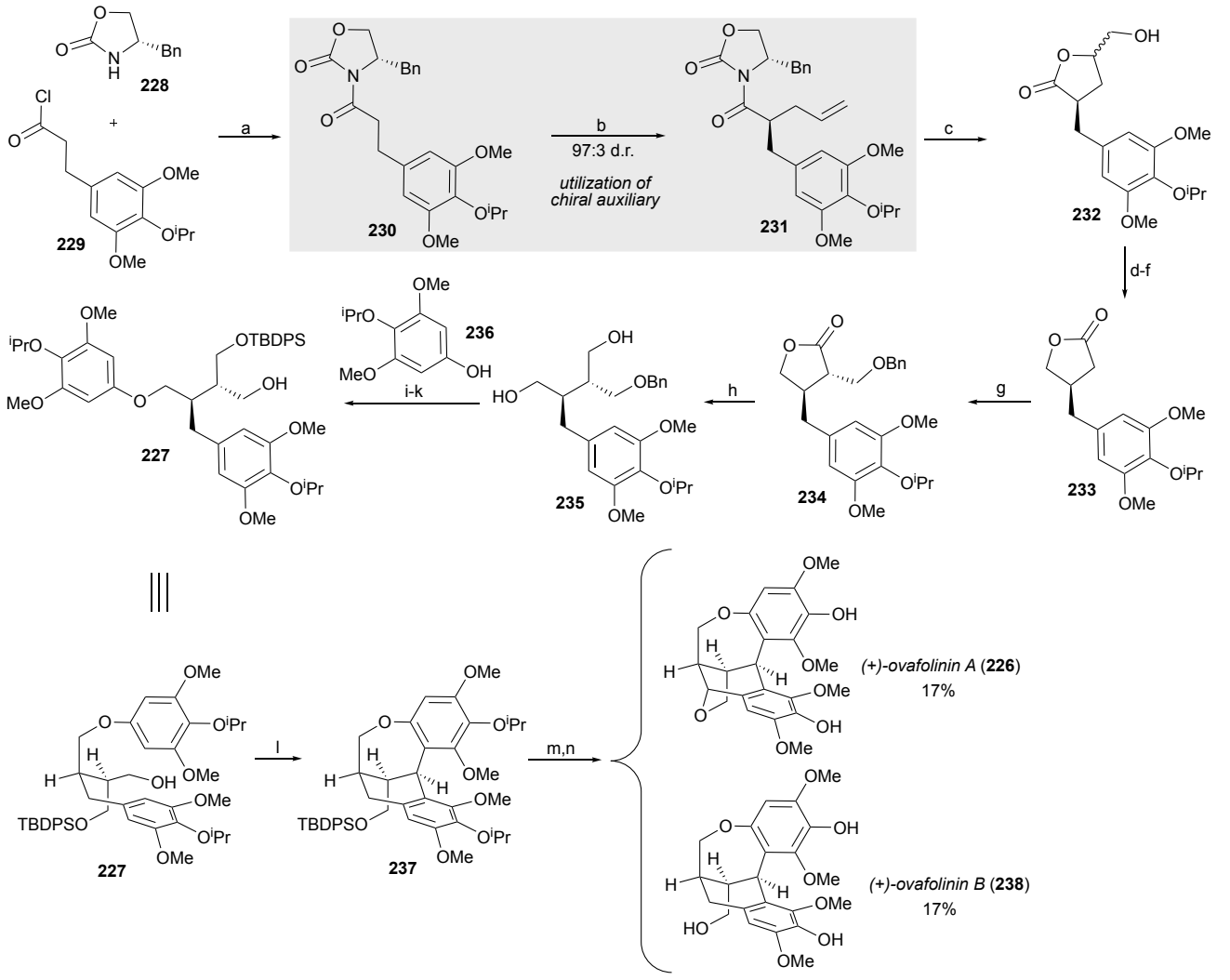
cyclolignan **16**, which underwent oxidation with CrO_3 and subsequent reduction with L-selectide to produce the target natural product **1** in five steps with a 28% overall yield. These methods were utilized on a variety of different substrates to produce (–)-polygamain, (–)-morelensin, (–)-austrobailignan 1, and (–)-hernandin, in addition to a regioisomer of (–)-deoxypodophyllotoxin and (–)-deoxysikkimotoxin, which are all closely related to (–)-podophyllotoxin (**1**).

3.1.4.12 Ovafolinins A and B

Barker's Synthesis: Barker and Davidson developed the first enantioselective total synthesis of (+)-ovafolinins A (**226**) and B (**238**) in 2017, using a cascade reaction sequence to concurrently form the benzoxepine moiety and the central six-membered ring systems. This approach involved the simultaneous formation of the C2–C7' and the C1'–C7' bonds (Scheme 66) from a 1,4-diarylbutane synthon, most similar to pathway ***D*** (Fig. 3A).[122] Evans chiral auxiliary **228** was added to acid chloride **229** to give oxazolidinone **230**, which was subsequently allylated to give olefin **231** with excellent selectivity (d.r. 97:3) (Scheme 67). Dihydroxylation yielded lactone **232**, and subsequent reduction and two oxidation steps gave lactone **233**. Introduction of a benzylmethyl group yielded **234** which was reduced to give diol **235** (d.r. >95:5). Diol protection followed by a Mitsunobu reaction with **236** and hydrogenolysis provided **227**. Subsequent oxidation with DMP allowed for the cascade reaction that formed the key C2–C7' bond and closed the external ring system to form **237**.



Scheme 66 Barker's synthetic strategy towards (+)-ovafolinins A and B.



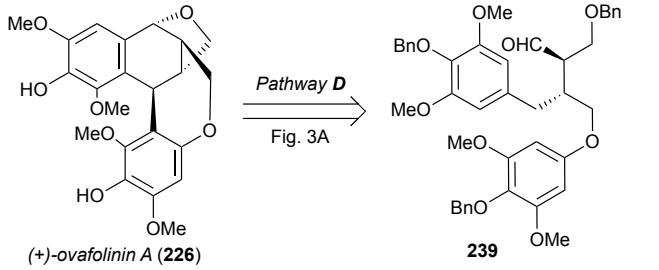
Scheme 67 Barker's total synthesis of (+)-ovafolinins A and B. a) *n*-BuLi (1.0 eq.), THF, −78 °C, 1 h, 74%; b) LiHMDS (1.2 eq.), allyl bromide (2.0 eq.), THF, −78 °C → r.t., 4 h, 78%, >97:3 d.r.; c) OsO_4 (1 mol%), NMO (2.0 eq.), *t*-BuOH, THF, H_2O, r.t., 44 h, 86%, 1.2:1 d.r.; d) $LiAlH_4$ (2.0 eq.), THF, 0 °C, 3 h; e) $NaIO_4$ (1.2 eq.), MeOH, H_2O, r.t., 1 h; f) Fétizon's reagent (1.4 eq.), PhMe, reflux, 5 h, 61% over 3 steps; g) BOMCl (1.2 eq.), LDA (1.1 eq.), THF, −78 °C → r.t., 18 h, 47%; h) $LiAlH_4$ (3.0 eq.), THF, 0 °C → r.t., 9h, 94%, 95:5 d.r.;. i) TBDPSCl (0.9 eq.), imidazole (1.1 eq.), CH_2Cl_2, r.t., 19 h, 67%; j) PPh_3 (1.2 eq.), DIAD (1.2 eq.), **236** (1.2 eq.), PhMe, 0 °C → r.t., 17 h, 88%; k) H_2, Pd/C (10 wt%), MeOH, r.t., 16 h, 34%; l) DMP (1.2 eq.), CH_2Cl_2, r.t., 1 h, 87%; m) $AlCl_3$ (5.6 eq.), CH_2Cl_2, 0 °C, 20 min, 79%; n) TBAF (3.3 eq.), THF, 0 °C → r.t., 2 h, **226** = 17%, 99:1 d.r, **238** = 17%, 99:1 d.r.

Deprotection steps gave a mixture of **226** and **238** (d.r. >99:1 for both) in 14 linear steps with an overall yield of 0.3%.

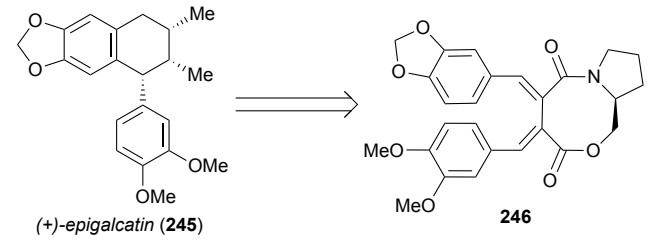
Hu's Synthesis: Inspired by Barker's work in 2017, Hu and coworkers developed a new and more efficient synthesis towards the formation of the architecturally complex (+)-ovafolinin A (**226**) and B (**238**).[123] Their final synthesis involved a double Friedel-Crafts reaction on a 1,4-diarylbutane synthon to concurrently form the C2–C7' and the C1'–C7' bonds (Scheme 68), most similar to pathway ***D*** (Fig. 3A). Syringaldehyde **240** was benzyl protected, then underwent reduction and bromination to afford **241** (Scheme 69). (*S*)-Taniguchi lactone ***ent*-21** was prepared via Kieseritzky's approach,[124] and was diastereoselectively alkylated to give **242** (d.r. >95:5). The lactone was opened, then reduced, and a Mitsunobu reaction with **243** afforded the phenyl ether **244**. Subsequent oxidation gave aldehyde **239**. A double Friedel-Crafts reaction successfully formed the key C2–C7' bond and closed the external ring system. Global debenzylation was done to afford (+)-ovafolinin B (**238**) in 11 linear steps with a 23% total yield. Benzylic etherification of **238** via the corresponding benzoquinone methide intermediate produced (+)-ovafolinin A (**226**) in 12 linear steps with a 21% total yield.

3.1.4.13 Epigalcatin

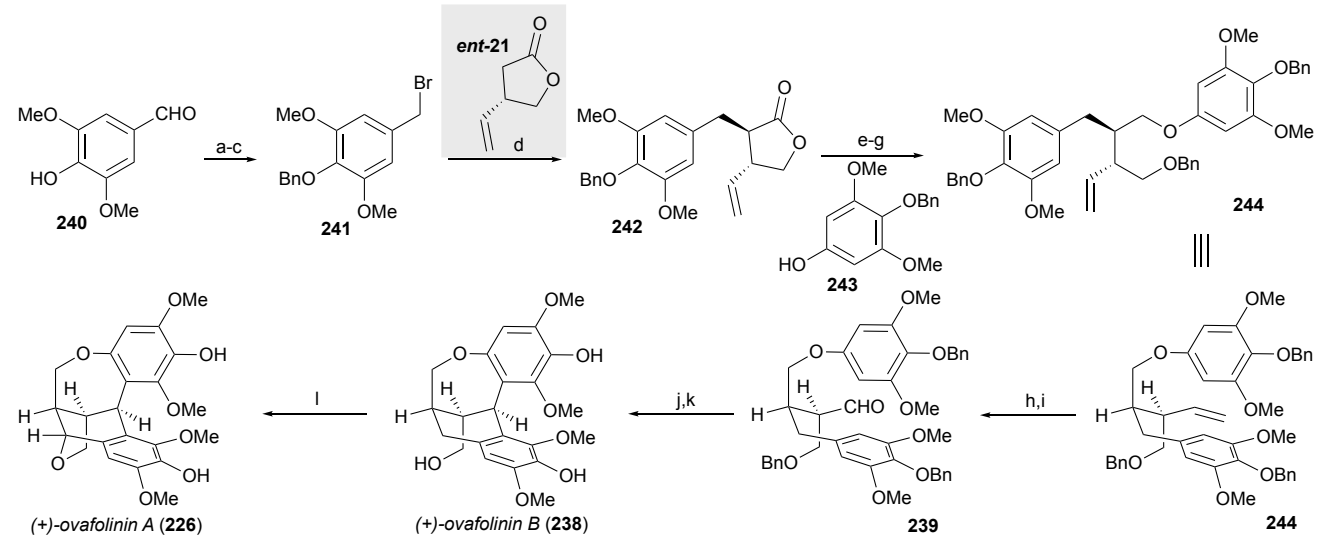
Czarnocki's Synthesis: (–)-Galcatin was first isolated in 1954 from the *Himantandra baccata* tree along with (–)-galbulin (**121**) and (–)-galbacin.[38] Its enantiomer, (+)-galcatin, was synthesized in 1981 by Liu and coworkers, and was found to be identical to the natural material in all aspects but optical rotation.[125] Each of these compounds possesses *trans* relationships between the stereocenters at C8 and C8', and C8' and C7', but Czarnocki was interested in accessing diastereomeric (+)-epigalcatin (**245**) with a *cis* configuration at the C8' and C7' stereocenters due to reports of those cyclolignans being more biologically active.[126] Accordingly, in 2018 Czarnocki and Lisiecki developed an enantioselective synthesis of (+)-epigalcatin (**245**) using the chiral auxiliary L-prolinol to control a key photocyclization step to form the C2–C7' bond via pathway ***D*** as shown in Figure 3A (Scheme 70, also refer to Scheme 35, 58).[127] As indicated in Scheme 71, a Stobbe condensation was used to combine diester **247** and aryl aldehyde **60** to afford *E,E*-bisbenzylidenesuccinic acid monomethyl ester **248**, to which the chiral auxiliary was added to afford amide **249**. A subsequent macrolactonization step produced the conformationally restricted amide **246**. The key photocyclization step proceeded smoothly using UV irradiation under flow conditions, to afford ester **250** after lactone methanolysis. Schwartz reagent was then used to remove the chiral auxiliary with excellent chemostereoselectivity. Following hydrogenation, Charlton's protocol was used to produce the alcohol **251**.[78] Converting the alcohol into the corresponding triflate allowed for a reductive displacement with $LiAlH_4$ to deliver (+)-epigalcatin (**245**) (d.r. >95:5) in 11 steps with a 5% total yield.



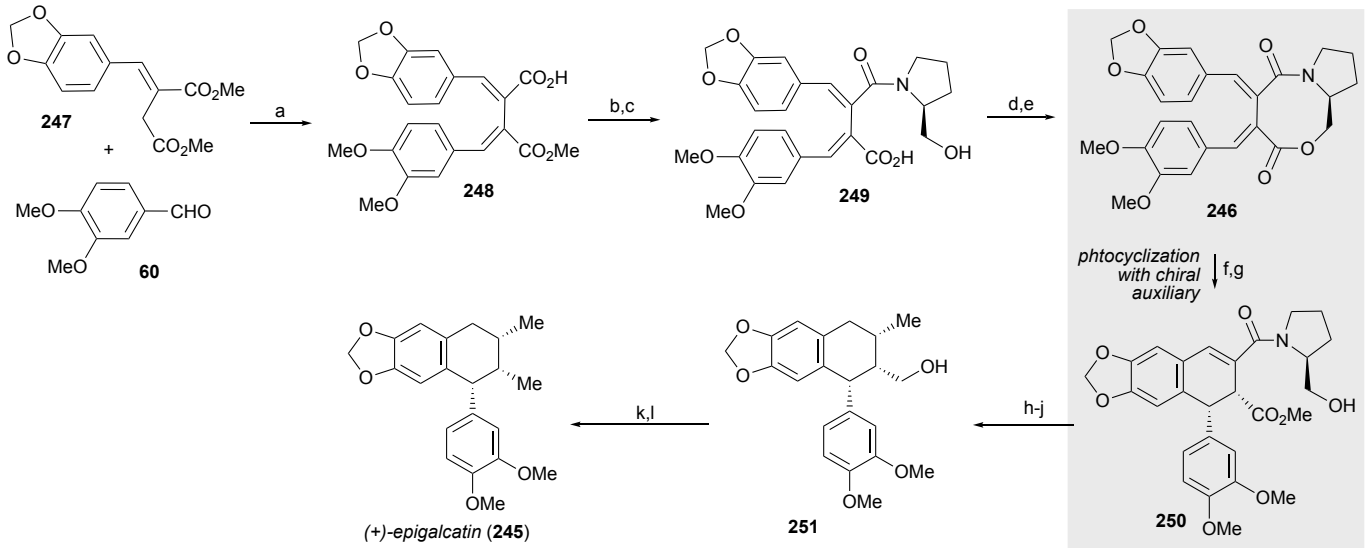
Scheme 68 Hu's synthetic strategy towards (+)-ovafolinins A and B.



Scheme 70 Czarnocki's synthetic strategy towards (+)-epigalcatin.



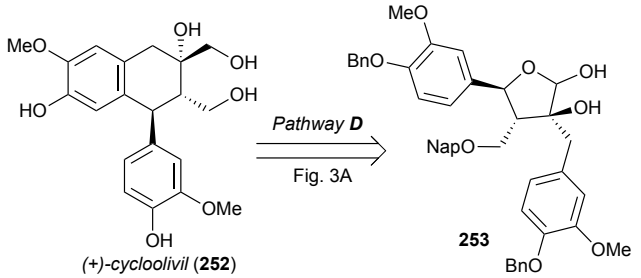
Scheme 69 Hu's total synthesis of (+)-ovafolinins A and B. a) BnBr (1.2 eq.), K_2CO_3 (1.2 eq.), DMF, r.t., 36 h, 92%; b) $NaBH_4$ (1.0 eq.), MeOH, CH_2Cl_2, 0 °C → r.t., 1 h; c) PBr_3 (1.0 eq.), CH_2Cl_2, 0 °C, 2 h, 72% over 2 steps; d) LiHMDS (1.2 eq.), THF, −78 °C → r.t., 1 h, 71%, >95:5 d.r.; e) KOH (5.0 eq.), BnBr (5.0 eq.), PhMe, 65 °C, 7 h, 78%; f) $LiAlH_4$ (1.2 eq.), THF, 0 °C, 99%; g) DEAD (2.0 eq.), PPh_3 (2.0 eq.), **243** (2.0 eq.), PhMe, Et_2O, r.t., 18 h, 94%; h) K_2OsO_4•$2H_2O$ (5 mol%), NMO (3.0 eq.), THF, H_2O, *t*-BuOH, 35 °C, 2 d; i) $NaIO_4$ (3.0 eq.), acetone, H_2O, r.t., 1 h, 77% over 2 steps; j) TFA (4.0 eq.), CH_2Cl_2, r.t., 1 h, 87%; k) Pd/C (10%), H_2, EtOH, EtOAc, r.t., 12 h, 99%; l) $Cu(OAc)_2$ (2.0 eq.), MeCN, 65 °C, 2 h, 91%.



Scheme 71 Czarnocki's total synthesis of (+)-epigalcatin. a) *t*-BuOK (1.1 eq.), PhMe, 2 h, r.t., 79%; b) $(COCl)_2$ (2.0 eq.),CH_2Cl_2, 0 °C → r.t., 2 h; c) Et_3N (3.0 eq.), L-prolinol (1.1 eq.), CH_2Cl_2, r.t., 1 h, 91% over 2 steps; d) K_2CO_3 (10 eq.), MeOH, H_2O, 80 °C, 8 h, 99%; e) BOP (1.5 eq.), Et_3N (3.0 eq.), CH_2Cl_2, r.t., 2 h, 65%; f) MeOH, TFA (0.01mM), *hν*, in-flow (0.7 ml/min); g) MeOH, HCl, 40 °C, 1 h, 65% over 2 steps; h) $Cp_2Zr(H)Cl$ (3.0 eq.), THF, r.t., 10 min, 65%; i) H_2, Pd/C (15 mol%), EtOH, r.t., 24 h, 76%; j) $LiAlH_4$ (6.0 eq.), THF, r.t., 1.5 h, 97%; k) Tf_2O (1.1 eq.), DIPEA (1.1 eq.), CH_2Cl_2, r.t., 1.5 h; l) $LiAlH_4$ (5.0 eq.), THF, r.t., 1.5 h, 54% over 2 steps, >98% ee.

3.1.4.14 Cycloolivil

Vakiti and Hanessian's Synthesis: While racemic cycloolivil was prepared in 1995 by the Iwasaki group,[128] Vakiti and Hanessian were first to report the enantioselective synthesis of (+)-cycloolivil (**253**) in 2020, along with several other lignans.[129] Their synthetic strategy made use of pathway ***D*** (Fig. 3A), generating the C2–C7' bond from a 1,4-diarylbutane synthon (Scheme 72). To begin their linear synthesis, vinylmagnesium bromide was added to 3-methoxy-4-benzyloxy benzaldehyde **254** to give allylic alcohol ***rac*-256**, which underwent a kinetic resolution with Novozyme[130] to deliver alcohol **256** and acetate **255** (Scheme 73). The ee values were not provided. Allylic alcohol **256** was carried forward in the synthesis by esterification with acryloyl chloride followed by a Grubbs first-generation catalyst-mediated ring-closing metathesis to give butanolide **257**, which was converted to lactone **258** through a conjugate addition of vinylmagnesium bromide. An aldol reaction with aldehyde **254** followed by ionic deoxygenation of the benzylic alcohol generated lactone **259** as a single isomer. Lemieux-Johnson oxidation and $NaBH_4$ reduction gave alcohol **260**, which was then naphthyl-protected prior to oxidation of the corresponding potassium-enolate with O_2. The resulting hydroperoxides were separated and treated with triphenylphosphine to give **261** and **262**, the latter of which was converted to (+)-cephafortin A (not shown) via catalytic hydrogenation. Alcohol **261** was carried forward by reduction with DIBAL-H to generate both triol **263** and hemiacetal **253**. While triol **263** was used to prepare (–)-olivil and (–)-alashinol G (not shown), hemiacetal **253** was used to generate (+)-cycloolivil (**252**). Treatment of **253** with $BF_3{\bullet}OEt_2$ and Et_3SiH generated oxonium ion **264**, which underwent *in situ* reduction to olivil before rearranging to the cyclolignan structure **265**. Catalytic hydrogenolysis of the protecting groups completed the synthesis of (+)-cycloolivil (**252**).

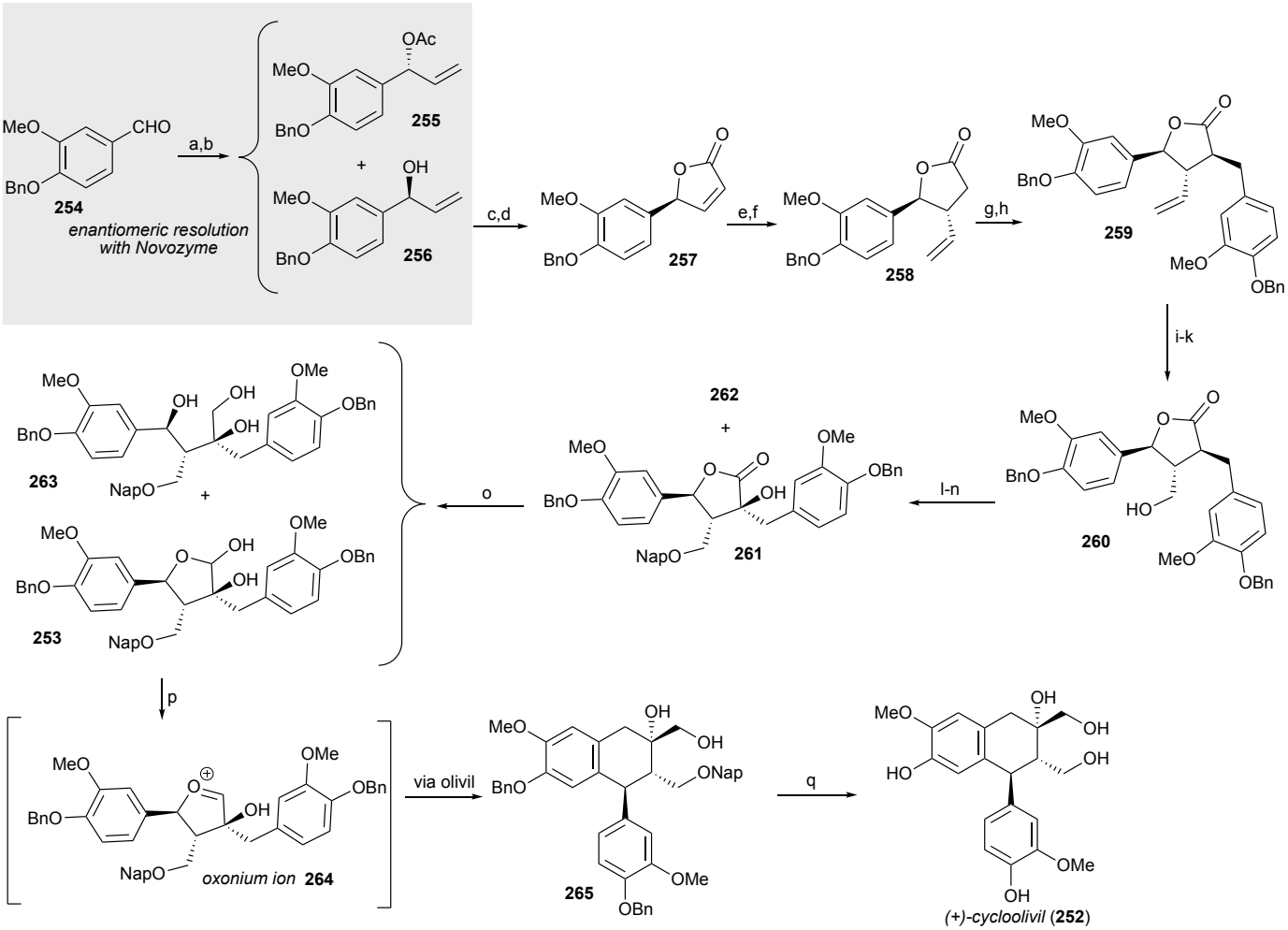


Scheme 72 Vakiti and Hanessian's synthetic strategy towards (+)-cycloolivil.

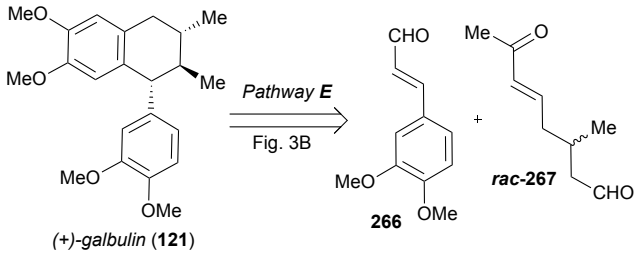
3.1.5 Disconnection E: Decalone to Naphthyl Ring Approach

3.1.5.1 Galbulin

Hong's Synthesis: Though syntheses of racemic galbulin have been previously achieved, most recently by Whitby[131] and Charlton,[78] Hong and coworkers described the first enantioselective total synthesis of (+)-galbulin (**121**) using an organocatalytic tandem double conjugate addition-aldol condensation cascade in 2012.[23] Their synthetic strategy, as illustrated through pathway ***E*** in Figure 3B, involves three unique bond disconnections about the cyclolignan skeleton: C1–C2, C3–C4, and C7'–C8' (Scheme 74). Furthermore, their approach represents an unusual strategy for preparing the naphthylene ring system through aromatization of an appropriately disposed decalone ring. Initially, a substituted pyran was treated with HCl and subsequently quenched with sodium bicarbonate to generate 3-methylpentanedial (Scheme 75). After addition of 1-triphenylphosphoranylidene-2-propanone, (E)-alkene ***rac*-267** was produced, which was subsequently allowed to react with aldehyde **266** using Jørgensen-Hayashi catalyst **201** to afford the double Michael reaction product **268** as the only observable stereoisomer (d.r. >95:5). Reduction, selective allylic oxidation, then epoxidation gave **269**. Further oxidation and aromatization yielded the requisite naphthylene skeleton **270**. Methylation of the free phenol within **270** followed by deoxygenation of the primary alcohol via its mesylate



Scheme 73 Vakiti and Hanessian's total synthesis of (+)-cycloolivil. a) vinylmagnesium bromide (1.2 eq.), THF, –78 °C, 2 h, 98%; b) isopropenyl acetate (4.0 eq.), Novozyme 435 (10% by wt.), PhMe, 4Å MS, 40 °C, 24 h, 90%; c) acryloyl chloride (2.0 eq.), Et_3N (6.0 eq.), DCM, 0 °C, 30 min; d) Grubbs 1st generation catalyst (10 mol%), CH_2Cl_2, 40 °C, 2 h, 71% over 2 steps; e) vinylmagnesium bromide (6.0 eq.), CuI (3.0 eq.), TMSCl (3.0 eq.), THF, –78 °C, 1 h; f) TBAF (1.0 eq.), THF, 0 °C, 1 h, 75% over 2 steps; g) **254** (1.5 eq.), LDA (1.0 eq.), THF, –78 °C, 1 h; h) Et_3SiH (4.0 eq.), $BF_3{\bullet}OEt_2$ (1.2 eq.), CH_2Cl_2, 0 °C, 2 h, 66% over 2 steps; i) OsO_4 (cat.), NMO (1.2 eq.), acetone, H_2O, r.t., 8 h; j) H_5IO_6 (2.5 eq.), THF, 0 °C, 1 h; k) $NaBH_4$ (2.5 eq.), THF, 0 °C, 1 h, 89% over 3 steps; l) 2-NapBr (1.5 eq), NaH (2.0 eq.), DMF, r.t., 1.5 h; m) KHMDS (1.4 eq.), O_2, THF, –78 °C, 1 h; n) PPh_3 (1.4 eq.), CH_2Cl_2, r.t., 2 h, 74% over 3 steps; o) DIBAL-H (6.0 eq.), PhMe, 0 °C, 3 h, 72%; p) $BF_3{\bullet}OEt_2$ (1.0 eq.), Et_3SiH (4.0 eq.), CH_2Cl_2, 0 °C, 10 min., 60%; q) 20% $Pd(OH)_2$ (100% by wt.), H_2, EtOAc, MeOH, r.t., 4 h, 98%.



Scheme 74 Hong's synthetic strategy towards (+)-galbulin.

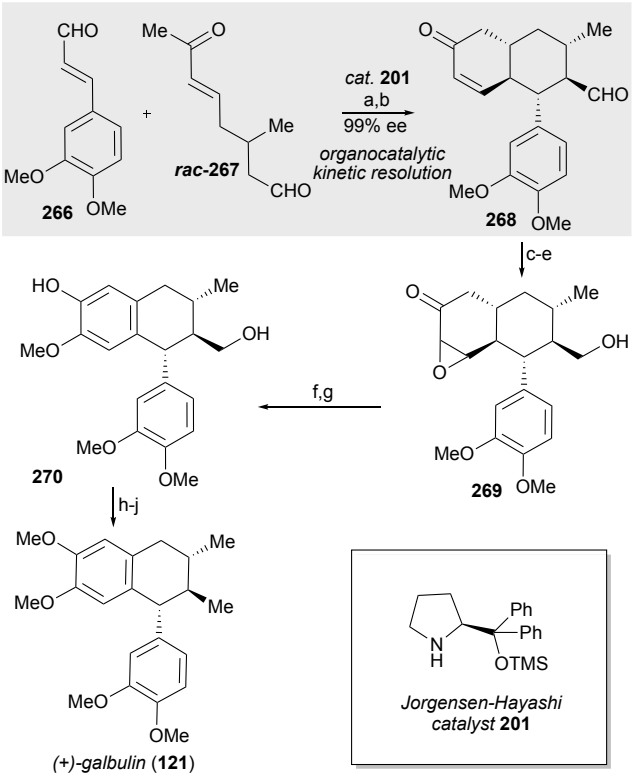
delivered (+)-galbulin (**121**) in 12 linear steps with an overall yield of 11%.

4. Conclusions

As demonstrated in the preceding sections, while the 1-arylnaphthalene core of the cyclolignans represents a relatively simple carbocyclic framework it lends itself to a surprisingly diverse range synthesis plans. In some instances, synthetic strategies have lent themselves to generalization and thus facilitated access to classes of related natural products in a unified manner. Conversely, other strategies represent singular examples that highlight the exceptional utility of a specific methodology in total synthesis. The enantioselective syntheses detailed here also serve to showcase the wealth of approaches available to chemists seeking to prepare natural products in optically enriched form. The particular challenges associated with these cyclolignans have inspired creative solutions and new chemical methodologies, and with new bioactive cyclolignans being isolated every year, synthetic interest in this family of natural products will likely continue to grow. As such, it will be interesting to see what new strategies, alternative disconnections, and useful synthetic methods reveal themselves in the future.

5. Abbreviations

2-ODD-PH 2-oxoglutarate-dependent dioxygenase



Scheme 75 Hong's total synthesis of (+)-galbulin. a) AcOH (0.2 eq.), cat. **201** (20 mol %), MeCN, r.t., 72 h; b) *p*-TsOH (1.6 eq.), MeCN, r.t., 5 h, 82% over 2 steps, 99% ee; c) $NaBH_4$ (1.3 eq.), $CeCl_3 \bullet 7H_2O$ (1.5 eq.), MeOH, 0 °C, 2 h; d) MnO_2 (15 eq.), CH_2Cl_2, r.t., 12 h, 98% over 2 steps; e) H_2O_2 (30%), NaOH (10%), MeOH, 0 °C, 2 h, 80%. f) KOH (3.5 eq.), MeOH, reflux, 10 min; g) 120 °C, 50 min, 44% over 2 steps; h) MeI (1.3 eq.), K_2CO_3 (2.0 eq.), acetone, r.t., 12 h, 95%; i) MsCl (2.0 eq.), Et_3N (2.0 eq.), CH_2Cl_2, r.t., 2 h; j) LiTEBH (2.3 eq.), THF, r.t., 80% over 2 steps.

3,5-DMP	3,5-dimethylpyrazole
Ac	acyl
AIBN	azobisisobutyronitrile
Ar	aryl
b.l.	branched to linear ratio
Bn	benzyl
BOM	benzyloxymethyl acetal
BOP	benzotriazol-1-yloxytris(dimethylamino)phosphorium hexafluorophosphate
Bpin	pinacol boronic ester
BPO	benzoyl peroxide
bpy	2,2′-bipyridine
brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
CDI	1,1'-carbonyldiimidazole
CFE	cell-free extract
CFL	compact fluorescent light
CHP	cumene hydroperoxide
CMPI	2-chloro-1-methylpyridinium iodide
CoA	coenzyme A
COD	cyclooctadiene
CSA	camphorsulfonic acid
DavePhos	2-dicyclohexylphosphino-2′-(N,N-dimethylamino)-biphenyl
dba	dibenzalacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N′-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
dF	difluoro
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPEA	N,N-diisopropylethylamine
DIPT	diisopropyl tartrate
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
DOSP	dodecylbenzenesulfonyl prolinate
dppf	1,1′-bis(diphenylphosphino)ferrocene
d.r.	diastereomeric ratio
dtbpy	4,4'-di-tert-butyl-2,2'-bipyridine
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
e.r.	enantiomeric ratio
Et	ethyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoroamide
IBX	2-iodobenzoic acid
$ipcBH_2$	monoisopinocampheylborane
LDA	lithium diisopropyl amine
LiTEBH	lithium triethylborohydride
m-CPBA	meta-chloroperoxybenzoic acid
Me	methyl
MOM	methoxymethyl
Ms	mesyl
MS	molecular sieves
N,N-DMBA	N,N-dimethylbenzylamine
Nap	2-naphthylmethyl
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
NMO	4-methylmorpholine N-oxide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PhMe	toluene
Piv	pivaloyl
PPTS	pyridinium p-toluenesulfonate
ppy	phenyl pyridine
Pr	propyl
PTSA	p-toluenesulfonic acid
pyr	pyridine
quant.	quantitative
r.t.	room temperature
SEM	trimethylsilylethoxymethyl
SM	starting material
(*S*,*S*)-TADOOH	[(4*S*,5*S*)-5-[hydroperoxy(diphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]-diphenyl-methanol
TBAF	tetra-n-butylammonium fluoride
TBD	triazabicyclodecene
TBDPS	tert-butyldiphenylsilyl
TBHP	tert-butyl hydroperoxide
TBS	tert-butyldimethylsilyl
TBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate
TEBAC	benzyltriethylammonium chloride
TEPA	tetraethylenepentamine

Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropyl
TMEDA	tetramethylethylenediamine
TMG	1,1,3,3-Tetramethylguanidine
TMOF	trimethyl orthoformate
TMS	trimethylsilyl
tol	tolyl
TRIP	3,3'-bis(2,4,6-triisopropylphenyl)-2,2'-binaphtholate
TRIS	tris(hydroxymethyl)aminomethane
Ts	tosyl

6. Author Contributions

R. G. Reynolds: Writing – original draft, writing – review & editing, visualization. H. Q. A. Nguyen: Writing – review & editing, visualization. J. C. T. Reddel: Writing – original draft, visualization. R. J. Thomson: Conceptualization, writing – review & editing, funding acquisition.

7. Conflicts of interest

There are no conflicts to declare.

8. Acknowledgements

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