Journal of Organic and Pharmaceutical Chemistry

Review Article

OPEN ACCESS
Freely available online on
http://ophcj.nuph.edu.ua

UDC [547.7+547.6]:54.057

F. Flóres-Hernández[1], T. I. Zárate-López[1], M. A. Alcaráz-Cano[2], J. Escalante[2], J. D. Rivera-Ramírez[1]

[1] Laboratorio de Química Farmacéutica, Departamento de Farmacobiología, Centro Universitario de Ciencias Exactas e Ingenierías Universidad de Guadalajara, 1421 Blvd. Gral. Marcelino García Barragán, Olímpica, 44430 Guadalajara, México

[2] Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, 1001 Avenida Universidad, 62209 Cuernavaca, México

Podophyllotoxin and Aryltetralin Lignans: Methods for the Synthesis of Rings *A, B, C, D*

Abstract

Podophyllotoxin, its derivatives and structural analogs are an extensive group of aryl-tetralin-lignans of interest in pharmacology due to their promising anticancer and antitumor activity. The synthesis methods proposed to date are aimed at solving synthetic, stereochemical, pharmacodynamic and environmental aspects. In this review, we have updated and brought together different classifications of lignan and podophyllotoxin synthesis. Transformation methods focus on the strategies used to form or functionalize rings A, B, C and D, as well as the configuration of the system of four stereogenic centers that fuse rings C and D.

***Keywords*:** lignans; podophyllotoxin; aryltetralin-lignans; etoposide; teniposide

Ф. Флорес-Ернандес[1], Т. І. Сарате-Лопес[1], М. А. Алькарас-Кано[2], Х. Ескаланте[2], Х. Д. Рівера-Рамірес[1]

[1] *Лабораторія фармацевтичної хімії, Департамент фармакобіології, Університетський центр точних наук та техніки, Університет Гвадалахари, бульвар Марселіно Гарсія Барраган, 1421, Олімпіка, м. Гвадалахара, 44430, Халіско, Мексика*

[2] *Центр хімічних досліджень, Автономний університет штату Морелос, Університетський проспект, 1001, Куернавака, 62209, Морелос, Мексика*

Подофілотоксин та арилтетралінові лігнани: методи синтезу кілець *A, B, C, D*

Анотація

Подофілотоксин, його похідні та структурні аналоги є великою групою арилтетралінових лігнанів, що становлять інтерес для фармакології, зокрема завдяки їхній багатонадійній протипухлинній дії. Методи синтезу, запропоновані сьогодні, спрямовані на вирішення синтетичних, стереохімічних, фармакодинамічних та екологічних аспектів. У цьому огляді ми оновили й об'єднали різні класифікації синтезу подофілотоксину та споріднених сполук. Обговорені методи зосереджені на стратегіях формування або функціоналізації кілець A, B, C і D, а також на конфігурації чотирьох стереогенних центрів, які поєднують кільця C і D.

***Ключові слова*:** лігнани; подофілотоксин; арилтетралінові лігнани; етопозид; теніпозид

Citation: Flóres-Hernández, F.; Zárate-López, T. I.; Alcaráz-Cano, M. A.; Escalante, J.; Rivera-Ramírez, J. D. Podophyllotoxin and aryltetralin lignans: Methods for the synthesis of rings A, B, C, D. *Journal of Organic and Pharmaceutical Chemistry* **2024**, *22* (2), 3–25.
https://doi.org/10.24959/ophcj.24.308942
Received: *23 July 2024*; **Revised:** *5 September 2024*; **Accepted:** *7 September 2024*

Funding: The authors thank the *Consejo Nacional de Humanidades Ciencia y Tecnología* (CONAHCYT) for the funding granted to carry out this research through the *Ciencia Frontera* project No. 610262 called "The chemo-enzymatic synthesis of podophyllotoxin-type lignans using green chemistry bases and their evaluation as probable antitumor compounds."
Conflict of interest: The authors have no conflict of interest to declare.

The Structure, Chemical and Pharmacological Properties of Podophyllotoxin

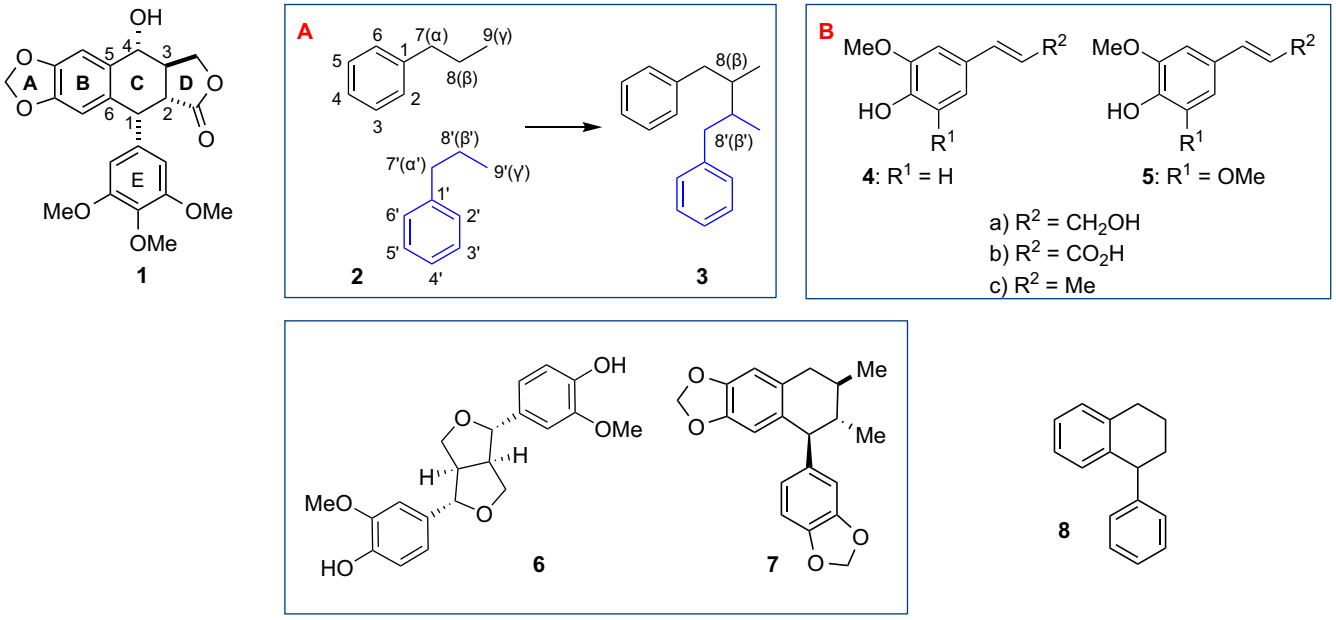
Podophyllotoxin (**1**) is the most prominent and abundant metabolite of the lignan family. It has been isolated from the roots, seeds, fruits and resins of plant species of the *Berberidaceae* family, mainly from the genus *Podophyllum* and *Bursera*. The first isolation dates to 1880 when *Poewyssotzky* obtained it from podophyllin resin [1, 2].

The description of a podophyllotoxin molecule uses structural, steric, and reactive criteria, which serve to determine aspects of transformation and design of the biological activity when derivatives and analogs are prepared. Structurally, podophyllotoxin is an aryltetralin lignan. Lignans are a family of secondary metabolites of the shikimic acid pathway and can be divided into four groups: lignans, neolignans, oxyneolignans, and lignanoids (trimers and analogs) [3]. Cyclolignans form the σ backbone when two phenylpropanoid units (C_6C_3) are linked through their respective positions 8, also called ß positions (this is a non-IUPAC nomenclature system based on their biogenesis; **2** and **3**, **Scheme 1**, *A*). In nature, phenylpropanoid units are found in the form of propenylphenols **4** and cinnamyl alcohols **5** (**Scheme 1**, *B*), which, *via* the enzymatic oxidation, form lignans of type **6** and **7** (**Scheme 1**, *C*). The prefix aryltetralin comes from the fact that podophyllotoxin contains a tetralin unit substituted with an aryl group (**8**). In the complete molecule of podophyllotoxin, it is possible to distinguish its five rings, which nomenclature was proposed by Moss [1]: the first four are fused, dioxolane (*A*), tetralin (*B* and *C*) and ß-lactone (*D*); for its part, ring *E* (3,4,5-trimethoxyphenyl) is linked to tetralin.

From the stereochemical point of view, four contiguous stereogenic centers can be distinguished in positions 7 (*R*), 8 (*S*), 7' (*R*), and 8' (*S*), which are denoted as 4, 3, 1, and 2, in accordance with the rules of systematic numbering for **1**. In this review, each position will be denoted referring to this last classification. Finally, it is possible to distinguish that the lactone ring (*D*) is fused to ring *C* in a relative *trans*-configuration.

From the pharmacological point of view, podophyllotoxin has been used for hundreds of years in traditional Chinese, Japanese, and Indian Ayurvedic medicine due to its antiviral and antitumor properties [2]. It has been used as an antidote against poisoning, as purgative, anthelmintic, and as a poison to treat venereal warts, and it has *anti*-HIV properties. By 1942, *Kaplan* reported the best treatment for that time of condylomata acuminata caused by the human papillomavirus [3]. By 1946, it was found that it could inhibit cell division and destroy rapidly proliferating cells due to its antimitotic and cytotoxic properties. Other reported activities include transcriptase inhibition, cardiovascular effects, immunomodulation, antileishmanial activity, high density lipoprotein activity, antifungal, antipsoriasis, antimalarial, antiasthmatic and *anti*-HIV activity [2].

The mechanism of action of podophyllotoxin is in microtubules. By binding to the colchicine



Scheme 1. The structure of podophyllotoxin (**1**), structural definitions of lignans (**2**, **3**, and **8**), and examples of lignans in nature (**4**, **5**, **6**, and **7**)

ISSN 2308-8303 (Print) / 2518-1548 (Online)

site of the beta-tubulin subunit, it prevents it from binding to guanosine triphosphate (GTP). Thus, by interrupting the formation and stabilization of the microtubules that make up the cytoskeleton of eukaryotic cells, it interrupts the formation of the mitotic spindle and causes destabilization of the microtubule structure in the G2/M phase (**Figure 1**) [3, 4].

In addition, podophyllotoxin is highly effective in the treatment of skin diseases, such as genital warts caused by the human papillomavirus (HPV), molluscum contagiosum and precancerous lesions, as well as it is highly potential as an anticancer agent due to its ability to stop cell division. Its antitumor activity has been proven in the treatment of Wilms tumors, genital tumors, non-Hodgkin lymphomas and lung cancer. However, its use for cancer treatment is limited since it is toxic and can cause serious gastrointestinal side effects, such as irritation, ulceration, pain, inflammation, and burns. For this reason, podophyllotoxin has been used as a precursor to obtain semisynthetic derivatives that are clinically applied as cytostatics in the treatment of various types of cancer [5].

Etoposide (**9**), teniposide (**10**) and etopofos (**11**) (**Figure 2**) are synthetic derivatives of podophyllotoxin with efficacy, enhanced selectivity, and low toxicity. They are used in chemotherapy against testicular cancer, lung cancer, and lymphoma, leukemia, Kaposi's sarcoma. However, they have such limitations as the development of drug resistance and myelosuppression.

These compounds have a structural base of aryltetralin lignans similar to podophyllotoxin. However, the differences are that the configuration of position 4 is opposite (*S*) and the substituent of that position is a protected glycosyl group. Additionally, etopofos contains a phosphate group in position 4' of ring E [6]. These structural variations generate a mechanism that is now based on the irreveersible inhibition of topoisomerase II, by forming a ternary DNA-topoisomerase-drug complex, which causes the accumulation of DNA-drug complexes. This prevents cell replication and transcription, causing double strand breaks in DNA and leading to apoptosis. Etoposide also shows other biological activities, such as cytotoxic, insecticidal, antifungal, antiviral, anti-inflammatory, neurotoxic, immunosuppressive,

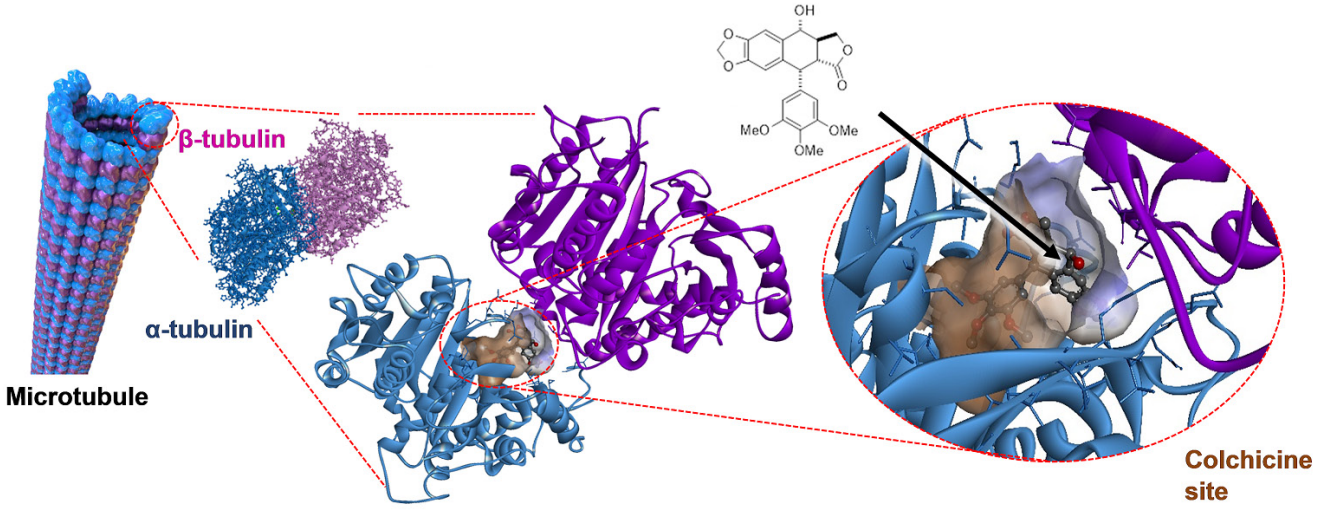


Figure 1. The representation of the position and constitution of microtubules in the eukaryotic cell and of the colchicine site in the β subunit of tubulin

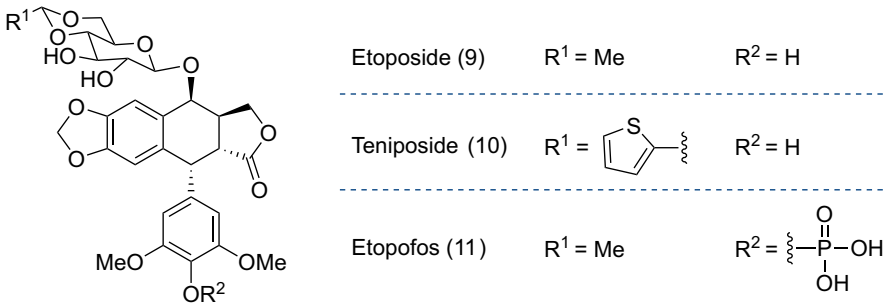


Figure 2. Chemical structures of etoposide (**9**), teniposide (**10**) and etopofos (**11**)

antirheumatic, antispasmogenic and hypolipidemic action [5].

These findings demonstrated the therapeutic potential of aryl-tetralin lignans and led to the development of a new class of antineoplastics known as podophyllotoxin analogs and derivatives. These compounds are used in combination with other chemotherapeutic agents to improve efficacy and reduce side effects of cancer treatments. In some cases, podophyllotoxin derivatives have been shown to be effective in treating cancers that are resistant to other chemotherapeutic treatments (**Figure 3**) [7].

Thus, an extensive multidisciplinary research network has been generated, so the demand for podophyllotoxin and its derivatives continues to increase. The proof of this is the growing number of works and research areas in this field. For the first half of 2023, for example, considering the search engines *Google academics* and *Concordia University Library*, the number of publications referring to podophyllotoxin until 2022 (a range of approximately 80 years) was around 4000 publications, approximately 50 publications per year. However, only in the period of 2022 to 2023 (18 months) approximately 700 publications were recorded with podophyllotoxin as a central topic, something like 39 monthly publications, at least one daily! By April 2024, around 500 articles had already been published on this topic, three per day.

The Synthesis of Aryltetralin Lignans Type Podophyllotoxin

The history of podophyllotoxin synthesis methods

In this bibliographic review, we will present a general overview of the efforts to obtain podophyllotoxin or one of its derivatives. This review of the most used synthesis methods is carried out, considering three aspects: (**a**) starting materials, (**b**) strategies to form rings *A*, *B*, *C* or *D* and (**c**) strategies for controlling the configuration of positions 1, 2, 3 and 4. Our aim is to generate a document that allows us to identify the existing methodologies for constructing strategic intermediate positions or structures, as well as the reaction conditions, catalysts, reagents, reaction media and efficient, rapid transformation sequences and economics that made them possible.

The race for the synthesis of podophyllotoxin and its derivatives began in the 1950s after a long accumulation of scientific evidence about its biological activity. The first methods for obtaining it used two strategies: the intramolecular *Diels-Alder* reaction (*vide infra*) and the epimerization of picropodophyllotoxin by racemization of position 2 *via* the formation of enolates. Through this latter methodology, diasteromeric mixtures of 45/55 of podophyllotoxin (**1**) and picropodophyllotoxin (**13**) were reported, which could be separated *via* crystallization with a yield of 38% of podophyllotoxin (**Scheme 2**). Years later, *San Feliciano* also used this strategy in the synthesis of podophyllotoxin [8, 9].

The second stage of these studies around the family of molecules began in the 1970s [10] with the first efforts to obtain the glycosylated analogs – etoposide [5], teniposide and etopophos [3]. Although the synthesis of these compounds is not related either the neolignan structure or the resolution of its stereogenic centers, or, on the other hand, their mechanism of action was not related to the synthesis of tubulin, but with topoisomerase, their notable therapeutic activity gave certainty to the pharmacological potential of their chemical structure and encouraged the search for new lignans.

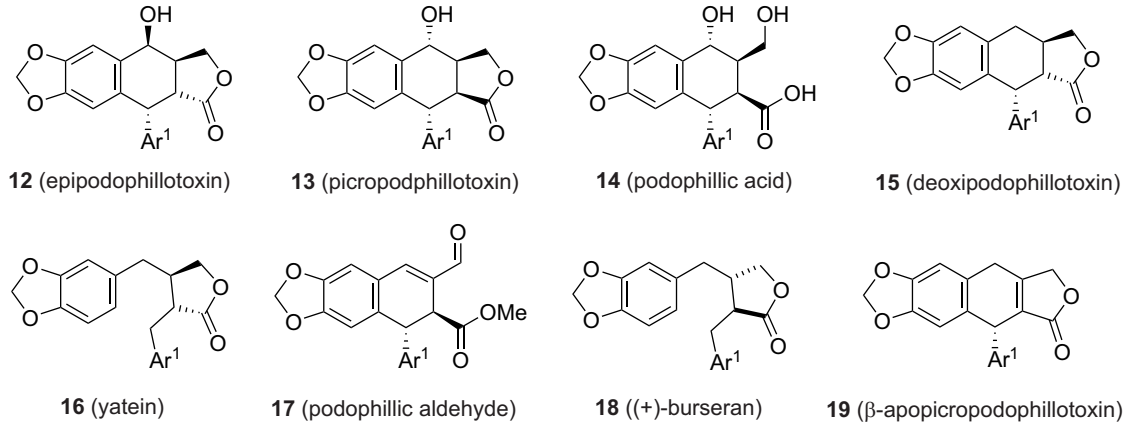
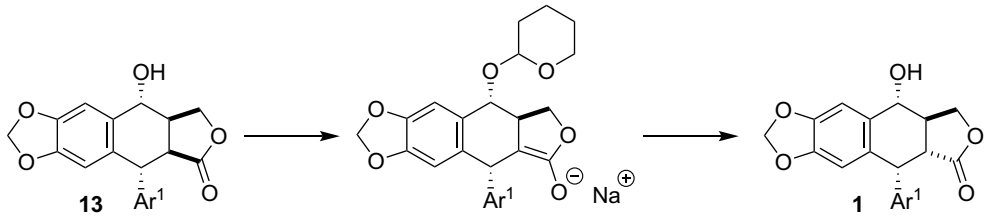


Figure 3. The podophyllotoxin analogs most studied from a pharmacological point of view

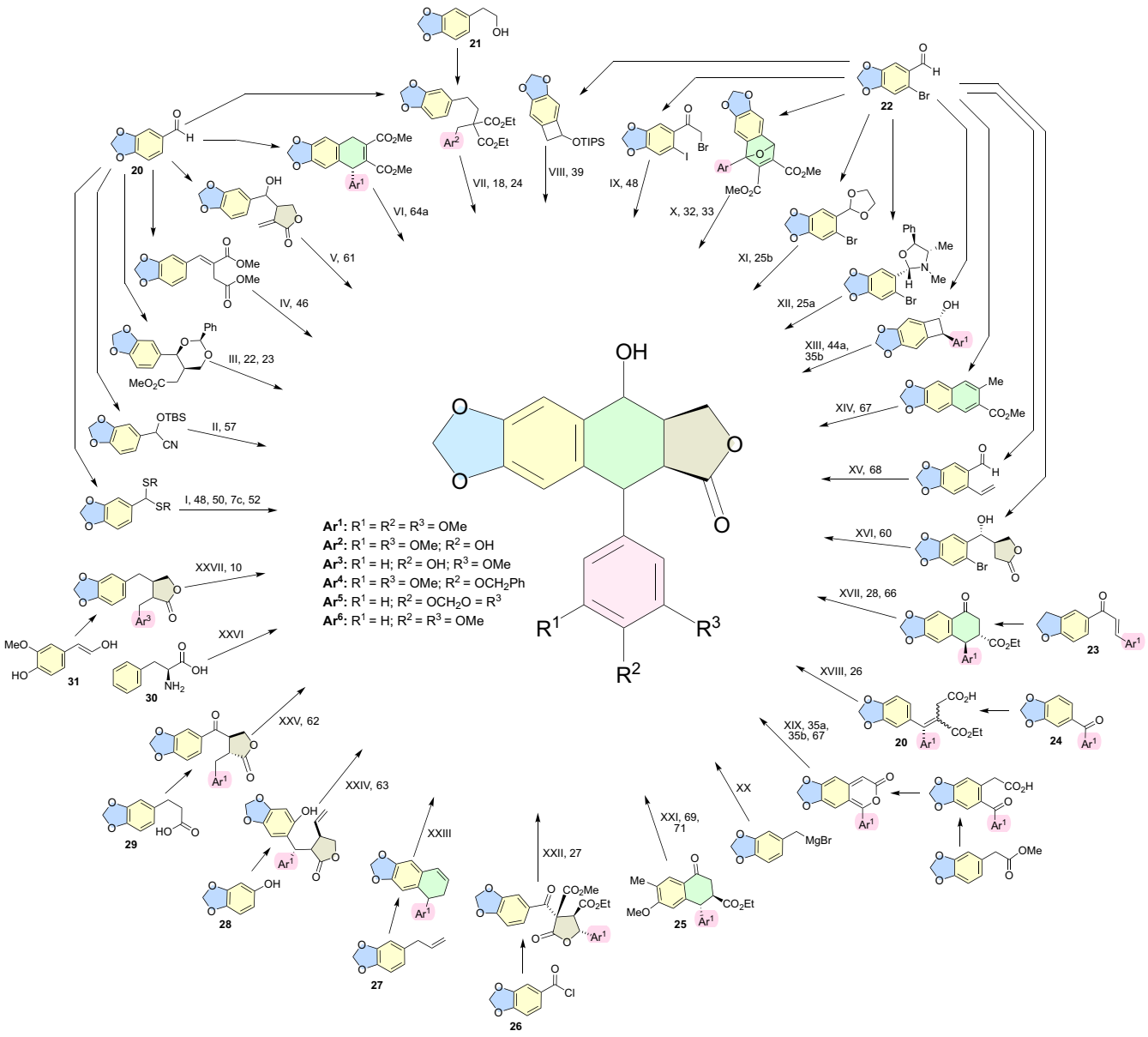
ISSN 2308-8303 (Print) / 2518-1548 (Online)



Scheme 2. Epimerization of picropodophyllotoxin (**13**), through the protection of the hydroxyl group with a pyranyl group, and sodium enolate formation to obtain podophyllotoxin (**1**)

The synthesis of rings *A* and *B*

The third stage was the search for total synthesis methods of podophyllotoxin and its analogs (**Scheme 3**). In 1991, *Ward* provided a valuable compilation of all the synthesis methods available up to that time and defined a general classification of four methods according to the type of transformation used, which was useful for later classifications. Thus, the methods of (**a**) oxoester, (**b**) hydroxyester, (**c**) *Diels-Alder*, and (**d**) conjugate addition, could be distinguished. These methods share two characteristics, each one focuses on the specific formation of ring *C* and, they all started from some derivative of 1,3-benzodioxol (methylenedioxyphenyl or piperonyl group). These starting materials have predominated in the search



Note: in Roman numeral the synthetic route; in Arabic numeral the bibliographic reference

Scheme 3. The main starting materials in the synthesis of aryltetralin lignan analogs of podophyllotoxin. Compounds with rings *A* and *B* fused are usually chosen.

for transformations and functionalization, and are the most useful since rings *A* and *B* are already fused. From this group of compounds, piperonal (**20**, also known as heliotropin), homopiperonyl alcohol (**21**), bromopiperonal (**22**), asymmetric aryl ketones derived from piperonal (**23** and **24**), vanillin derivatives (**25**), piperonyl chloride (**26**), safrole (**27**), sesamol (**28**), 3,4-methylenedioxydihydrocinnamic acid (**29**), phenyl alanine (**30**), and coniferyl alcohol (**31**) are the most prominent prototypes, in which it is possible to carry out transformations of positions 5 or 6 of ring C (*see* **Scheme 1**). Due to their relative abundance in nature, few reports have focused on their synthesis during the search for aryltetralin lignans. The reports by *Urlacher* [11] and *Sattely* [12] are notable since it was possible to synthesize ring *A*, to subsequently obtain deoxypodophyllotoxin (**15**) and podophyllotoxin (**1**) from coniferyl alcohol or phenylalanine, and a cascade of modified metabolic reactions.

Other precursors similar to this group of compounds are vanillinic acid and vanillin, which despite lacking ring *A*, have been used to synthesize structural analogs of podophyllotoxin.

There are useful methods for forming the 1,3-dioxol ring on phenyl rings: for example, the reaction between 1,2-diphenols (catechols) and methylene bromide [13], methylene chloride [14], or methyl enolates [15]. The reaction of *ortho*-quinones and imines catalyzed by palladium to obtain substituted 1,3-dioxol rings [16] or obtaining of piperonal using black pepper piperonal synthase has also been reported [17]. The reactivity relationships of the positions attached to the aromatic ring between safrole, isosafrole, piperonal and sesamol have been studied; starting from catechol, it is possible to find safrole and isosafrole as intermediates until reaching piperonal, from which, in turn, protocols have been described to obtain sesamol [18–21].

Regarding alternatives to functionalize the 1,3-benzodioxol system in the search for aryltetralin lignans, we can generalize two cases:

1. One can take advantage and transform a substituent into the 1,3-benzodioxol system, which carbon will be the position 4 of the arylteralin lignan. A side substituent has generally been a benzylic position in the form of carbonyl or primary and secondary alcohol that will become positions 2 and 3. Piperonal (**20**) and bromopiperal (**22**) (**Scheme 2**, transformations I to XVI) are the most used reagents for this purpose. In these compounds the carbonyl group is transformed into the secondary alcohol of position 4, also accompanied by reactions that introduce the carbons of positions 2 and 3 whether they include ring *D* or not. Other useful substrates to follow this transformation route are those used in transformations VII, XIX, XX, XXI, XXII, XXIII, XXV and XXVII. When it comes to asymmetric syntheses or resolution, this transformation route has served to assemble molecule with the necessary configuration in positions 3 and 4.

2. A less studied route starts from 1,3-benzodioxols with a substituent that in subsequent transformations would be position 1 of the tetralin-lignan. This is probably because it would involve choosing or preparing a diarylmethanyl system, which means more synthetic steps to reach the corresponding aryltetralin lignan. The formation of these types of bonds is usually designed to occur in the intermediate or final stages of the most of synthetic routes (*see* **Scheme 4**). In the literature it is possible to find examples of transformations XVIII and XXI.

The methods of constructing ring *C*

As mentioned before, most of the variants for the synthesis of aryltetralin lignans focus on the construction of ring *C*. This way makes it possible to configure the four stereogenic centers of the lignans. From the pharmacological point of view, variations in positions 1 and 4 have shown good results. In general, the closure of ring *C* is the final step of a variety of transformations, in which we can distinguish the following three cases:

A. *dihydroxyester and oxoester strategies* – the ring closure through the formation of a diarylmethanyl bond between position 1 of the tetralin system and position 6 of the 1,3-benzodioxol ring (**Scheme 4**, *A*);

B. the ring closure through Diels-Alder cycloadditions (**Scheme 4**, *B*);

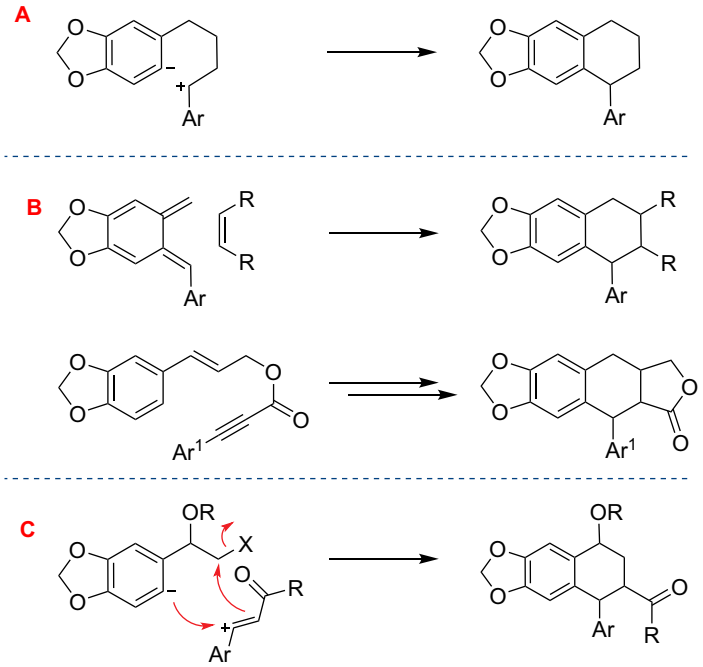
C. *the conjugated addition* – the ring closure through a cascade of Michael-type reactions and the nucleophilic substitution by α anions (**Scheme 4**, *C*).

The next three sections focus on the most useful examples of these strategies.

Strategy A. Dihydroxyester and oxoester strategies

One of the first contributions was the work of *Curran* [22] where the key intermediate was a 1,3-dicarbonyl system (**32**). Here, the α carbon will become that of position 2 of the tetralin lignan, which is also in position ß (or position 1 of the tetralin lignan, which is also a benzylic carbon) has attached to ring *E* in some of its variants

ISSN 2308-8303 (Print) / 2518-1548 (Online)



Scheme 4. The ring C closure strategies in the synthesis of aryltetralin lignans: **(A)** formation of the bond between positions 6 and 1; **(B)** the *Diels-Alder* cycloaddition; **(C)** the *Michael* reaction cascade – nucleophilic substitution by enolates

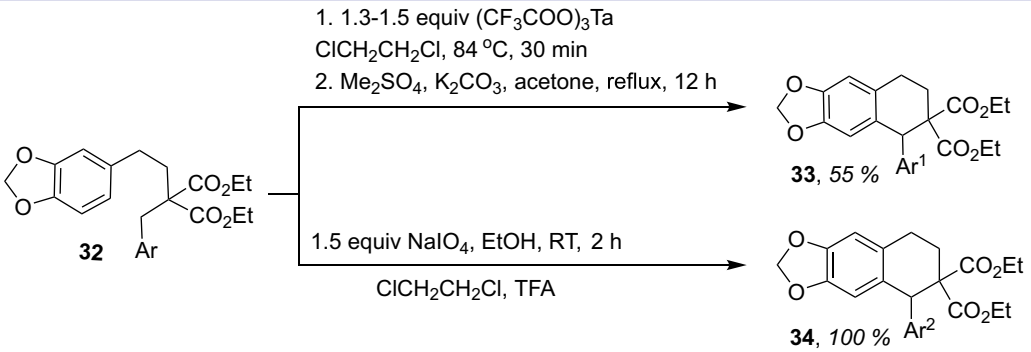
(*see* **Scheme 3**). Thus, with the formation of the bond between position 6 and 1 through two different strategies, ring *C* (**33** and **34**) is formed (**Scheme 5**).

A strategy similar to that of *Curran* regarding the closure of ring *C* has been used independently by *Daugan* [26], *Koga* [27], and *Uda* [28] for the construction of deoxypodophyllotoxin epimers (**15**). The key step of these three transformations is the formation of the two enantiomers of intermediate **35** obtained by resolution and enantioselective synthesis. Thus, with the transformation of each enantiomer, the corresponding epimer **36** was obtained, and after resolution the epimers of **15** were generated, where the final step of synthesis was the formation of ring *C* since rings *A*, *B* and *D* were previously incorporated (**Scheme 6**).

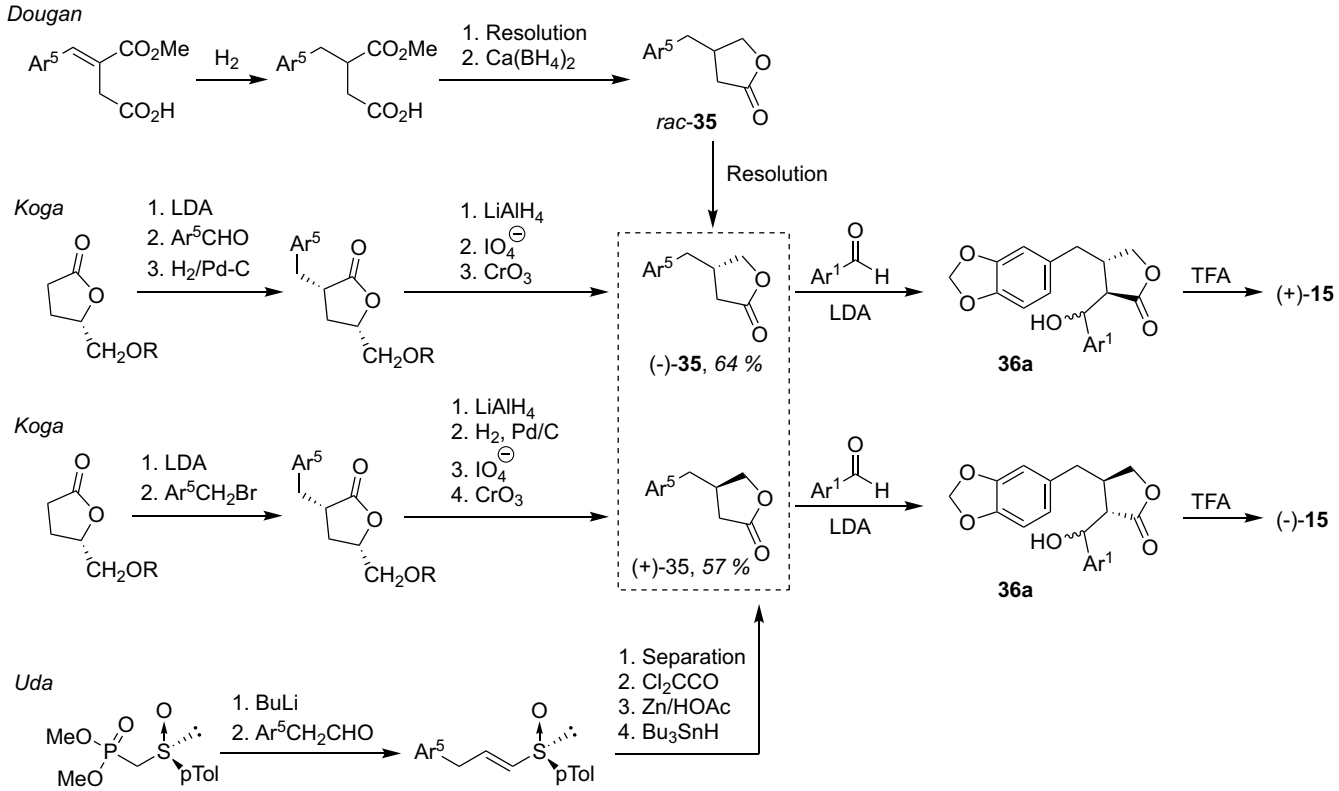
Vandewalle proposed the same ring *C* closure method using protected diols in the form of 1,3-dioxane [29] as a preliminary method and silylene ether (**37**) [30] integrated into positions 2 and 4 of tetralin. In turn, this substrate contains a carbonyl group in position 2. Through the aldol addition to an aryl aldehyde, position 1 and ring *E* are incorporated. The result is position 2 activated for the nucleophilic substitution (**38**) by the aryl carbon of position 6 that will close ring *C* (**Scheme 7**).

As can be seen, 1,3-dicarbonyl-α,ß-unsaturated systems that have ring *E* attached to position ß (position 1 of aryltetralin lignan) is a key substrate to carry out this type of the cycle closure. *Curran* noted this advantage by proposing the Michael addition between the piperonal-derived Michael donor and the Michael acceptor **39** where the intermediate α anion carried out the intramolecular nucleophilic substitution resulted in the formation of ring *C* of compound **40** (**Scheme 8**) [31].

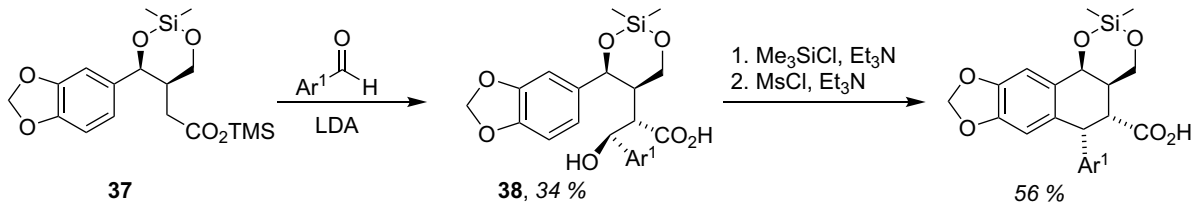
A similar strategy was proposed by *Zhang* [32, 33], in which a piperonal bromine derivative (**41**)



Scheme 5. The ring C closure proposed by *Curran*



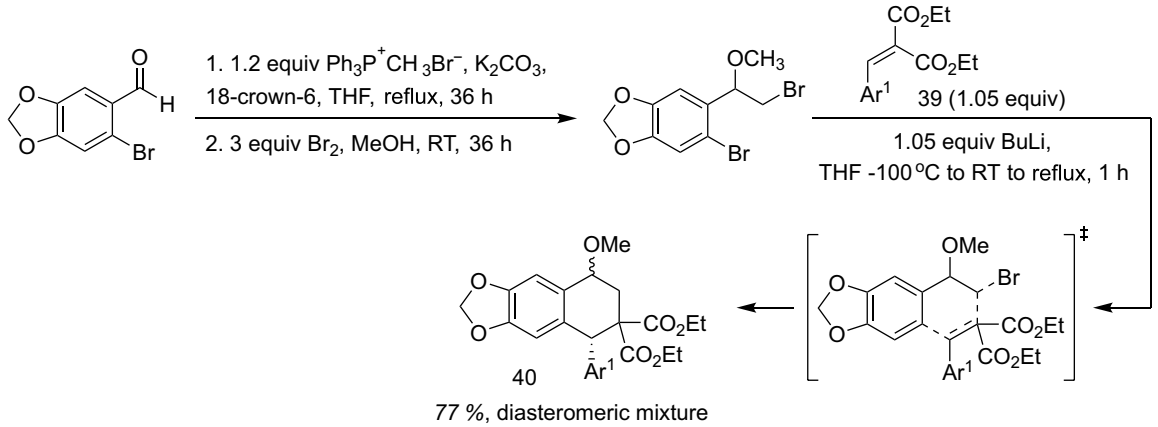
Scheme 6. The ring C closure for the synthesis of deoxypodophyllotoxin epimers (**15**)



Scheme 7. The ring C closure via the nucleophilic substitution in position 2

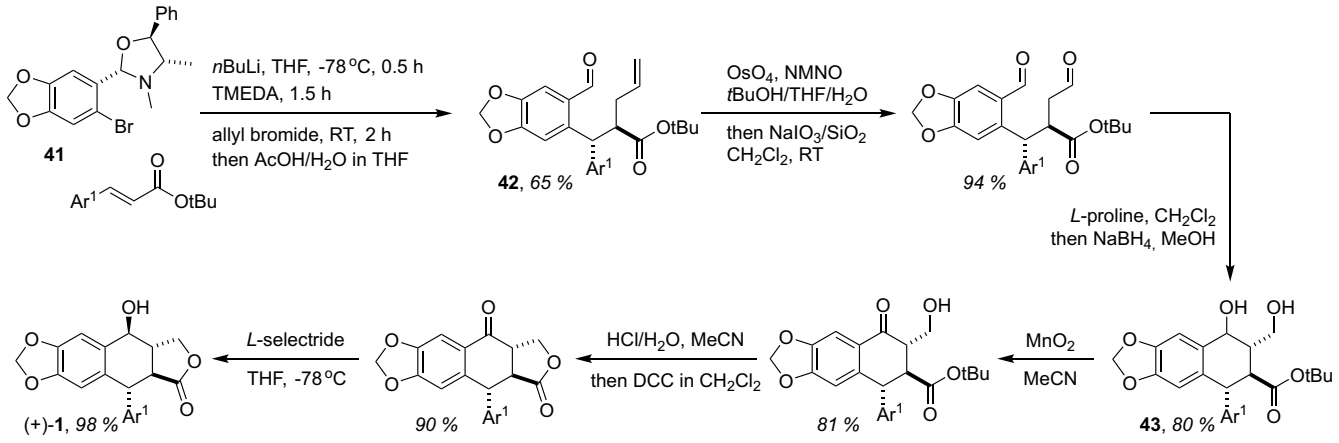
protected with a chiral pseudoephedrine auxiliary carried out the *Michael*-type reaction with an acceptor containing ring *E* (**Scheme 9**). A sequential process of the *Michael* addition and nucleophilic substitution were used to incorporate an allyl group in the α-position to obtain intermediate **42**. Its oxidation generated the corresponding dialdehyde used further for the cyclization of ring *C via* the aldol addition to obtain intermediate **43**. The formation of ring *D* was carried out *via* the lactonization to obtain podophyllotoxone with the subsequent reduction generated the podophyllotoxin enanitomer ((+)-**1**).

The extensive oxoester pathway constructs ring *C* in the form of a γ-oxoester intermediate **44** (**Scheme 10**). This strategy was originated by

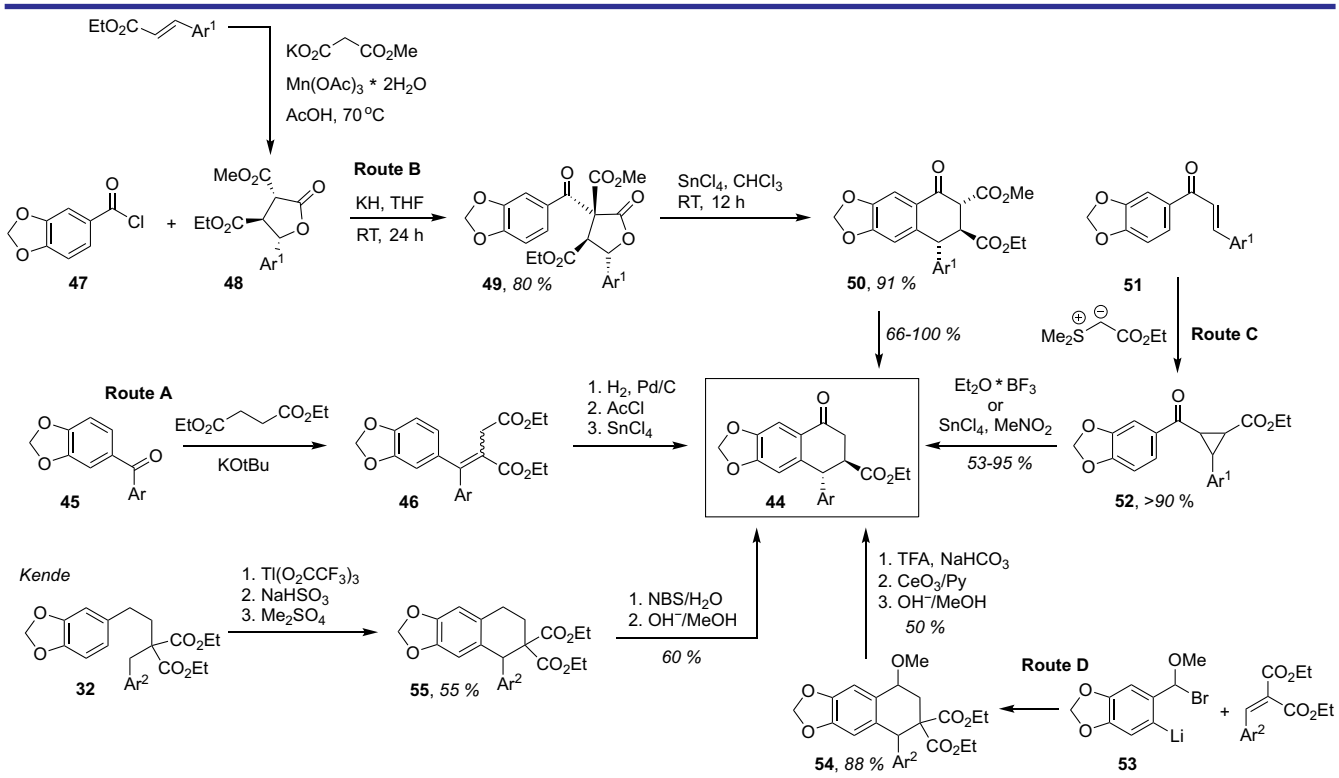


Scheme 8. The ring C closure using the *Michael* addition and aldol reaction sequence

ISSN 2308-8303 (Print) / 2518-1548 (Online)



Scheme 9. The synthesis of podophyllotoxin and its enantiomer proposed by *Zhang*



Scheme 10. The oxoester pathway in constructing ring *C* of aryl tetralin lignans

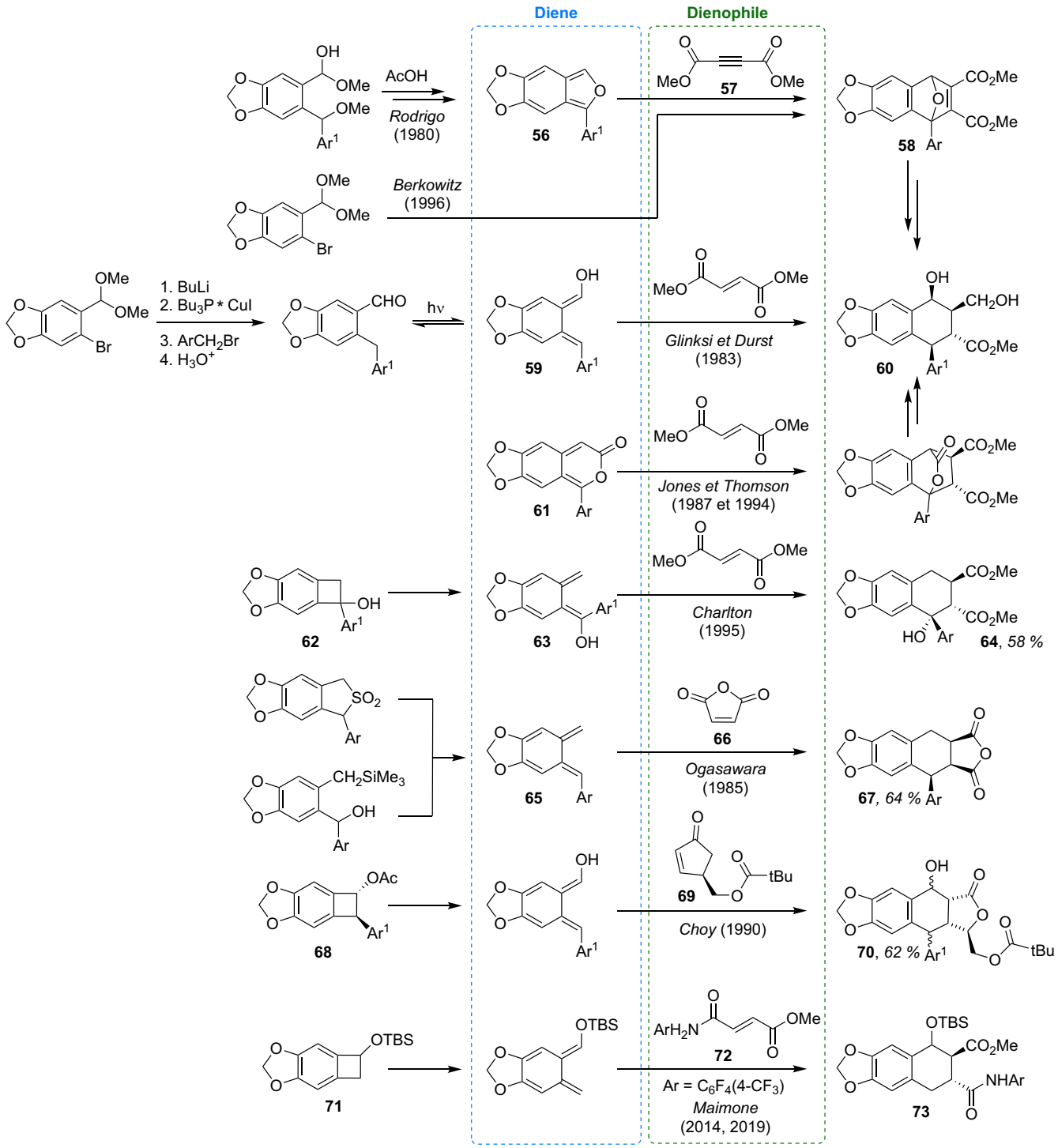
Gensler (*Route A*) [34] with the construction of ring *C* through the aldol condensation between diaryl ketone **45** and diethyl succinate to generate **46**, upon which the ring closure was carried out *via* the *Friedel-Crafts* type acetylation. *Rogers* designed γ-aryllactone **48**, which enolate carried out the addition-elimination on piperonyl chloride **47** and generated intermediate **49**, which, after the rearrangement and decarboxylation (**50**), gave the oxoester intermediate (*Route B*) [35]. For their part, *Wattanasin* [36] and *Doyle* [37] (*Route C*) proposed the formation of trisubstituted cyclopropyl intermediate **52** from α,ß-unsaturated piperonyl ketones **51** for constructing the corresponding oxoesters **44**. *Curran* (*Route D*) also proposed the formation of type **44** oxoesters in two independent methodologies. The first is based on his own previous contributions from the 1,3-dicarbonyl system (**32**) [38], and the second from a methoxybromide (**53**) derived from piperonal to generate **55,** a structural analog of **33** [29].

Strategy B. Addition via the Diels-Alder reaction

Another route for the construction of ring *C* is through the Diels-Alder reaction remained in force for almost 50 years. One of its advantages is that it allows almost all alternative configurations of the tetraline system to be addressed. From the synthetic point of view, the diene occurs in a variant of the system that already contains the methylenedioxyphenyl nucleus (rings *A* and *B*), either as a resonance hybrid or as a formal structure

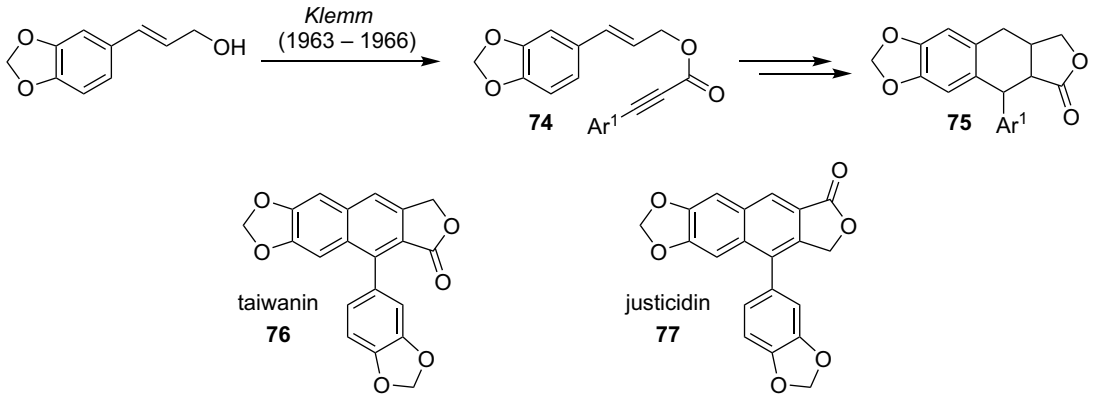
that is in equilibrium with a precursor. Thus, the most notable contributions offer alternatives for the design of dienophiles that allow the construction or almost complete incorporation of rings *D* and *E*.

For the purposes of studying the Diels-Alder pathway, we can divide the contributions into intermolecular reactions (**Scheme 11**) and intramolecular reactions (**Scheme 12**). Many intermolecular methods use dimethyl fumarate or its analogs as dienophiles, in which precursors of aryltetralin lignans are obtained where rings *A*, *B*, *C*, and *E* are already included, and ring *D* will be formed later. Thus, one of the first contributions was proposed by *Rodrigo* [39] through the formation of an isobenzofuran ring substituted in position 1 with ring *E* (**56**). This system functioned as a diene and reacted with dimethyl acetylenedicarboxylate (DMAD, **57**) generating an adduct already containing the aryltetralin-lignan system (**58**). This adduct was also formed by *Berkowitz* by a similar synthesis route [40].



Scheme 11. Examples of an intermolecular Diels-Alder reaction in the synthesis of aryltetralin lignans

ISSN 2308-8303 (Print) / 2518-1548 (Online)



Scheme 12. The example of the intramolecular Diels-Alder reaction in the synthesis of aryl-tetralin lignans

Another method was proposed by *Durst* [41] forming a diene *via* irradiation promoting the tautomeric equilibrium between a piperonal derivative and the corresponding enol (**59**). The latter when reacting with dimethyl fumarate generates the adduct with ring *C* formed (**60**). This product and its analogs and precursors were also obtained by *Thomson* [42, 43] in his strategy from a diene in the form of isochromenone (**61**) which also reacts with dimethyl fumarate.

Charlton [44] for his part, used benzocyclobutanol (**62**) to form an enol-type diene (**63**) reacted with dimethyl fumarate to generate a product similar to the *Durst*'s substituted with a hydroxyl group in position 1 (**64**).

The last two intermolecular Diels-Alder strategies employ α,ß-unsaturated cyclopentacarbonyls as dienophiles. This alternative has the advantage that the products obtained are tetralin lignans, analogs of podophyllotoxin with the five integrated rings. *Ogasawara* [45] used maleic anhydride (**66**), which, when reacted with dimethylenecyclohexa-1,3-diene (**65**), generated the deoxypodophyotoxin analog **67**. In this methodology, it is notable how the diene can be obtained from two different substrates. *Choy* [46] used a dienophile integrated with a chiral auxiliary (*R*)-(4-oxocyclopent-2-en-1-yl)methyl pivalate (**69**), meanwhile the diene (similar to **59**) was generated in a strategy similar to that of *Charlton* frombenzocyclobutanol (**68**). In this case, the product obtained was a mixture of picropodophyllotoxin epimers (**70**). Finally, the *Maimone*'s [47, 48] strategy used benzocyclobutanol **71** and the fumarate derivative **72** to obtain product **73** similar to **60**.

Although the intermolecular Diels-Alder reactions for constructing podophyllotoxin and its analogs are the most versatile and widespread, first the corresponding intramolecular variants were developed. A generic example is represented by the synthesis of lignan lactones **75** *via* the Diels-Alder reaction in which both the diene (*E*-propyl styrene system) and the dienophile (an α,ß-unsaturated ester that in the ß position is linked to the corresponding *E* ring) are present in the same substrate (**74**) [49–53]. It highlights the synthesis of the substrates through the classical *Fischer* esterification [54] and various ways of activating the corresponding Diels-Alder addition, such as microwave irradiation [55]. This strategy has been used to synthesize tetralin lignans, such as taiwanin (**76**) and justicidin (**77**) (**Scheme 12**) [56].

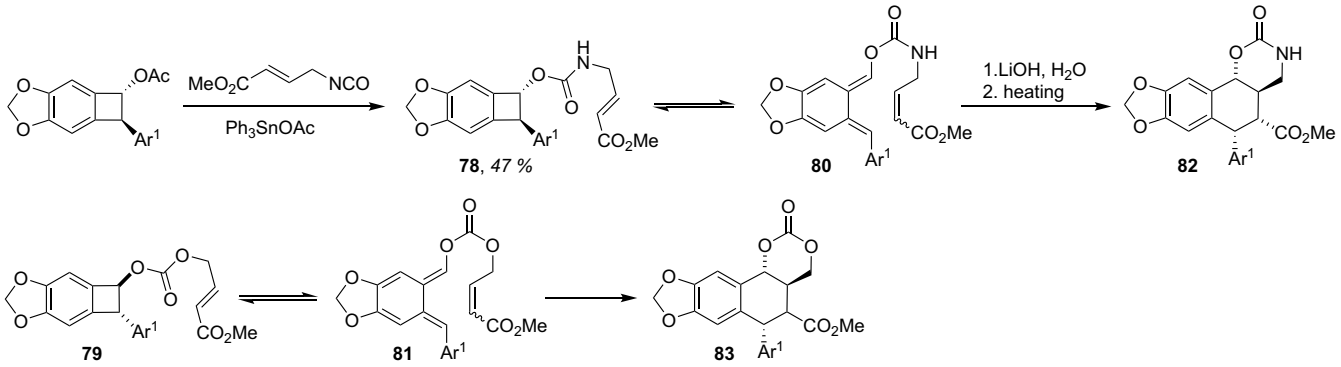
Thus, proposals for the synthesis of podophyllotoxin through an intramolecular Diels-Alder reaction have been presented regularly. *Durst* and *Speltz* reported two strategies. From carbamates (**78**) [57, 58] and carbonates (**79**) [59] they generated dienes similar to those prepared by *Choy* and *Charlton* (**80** and **81**) and cyclized to generate ring *C* (**82** and **83**, **Scheme 13**).

Czarnocki [60] also provided his version of a pericíclic reaction to form ring *C* using prolinol as a chiral auxiliary. Intermediate **84** underwent an electrocyclic reaction that generated compound **85** (**Scheme 14**).

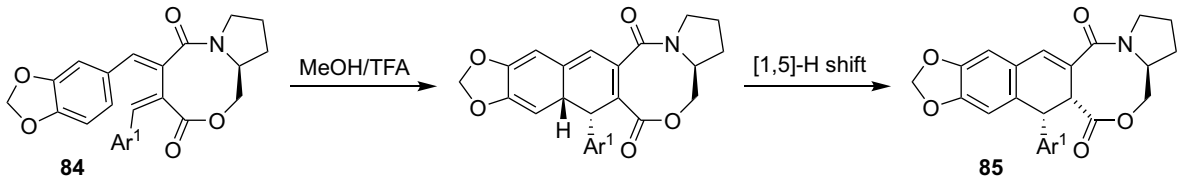
Strategy C. Conjugate addition

Another widely used and standardized methodology in constructing ring *C* is activating position 4 as a nucleophile. This strategy can be carried out through α-carbon reactions, Knoevenagel-type reactions, or activations *via* the Corey-Seebach or other umpolung reactions, which have been the most efficient and selective in this group of transformations.

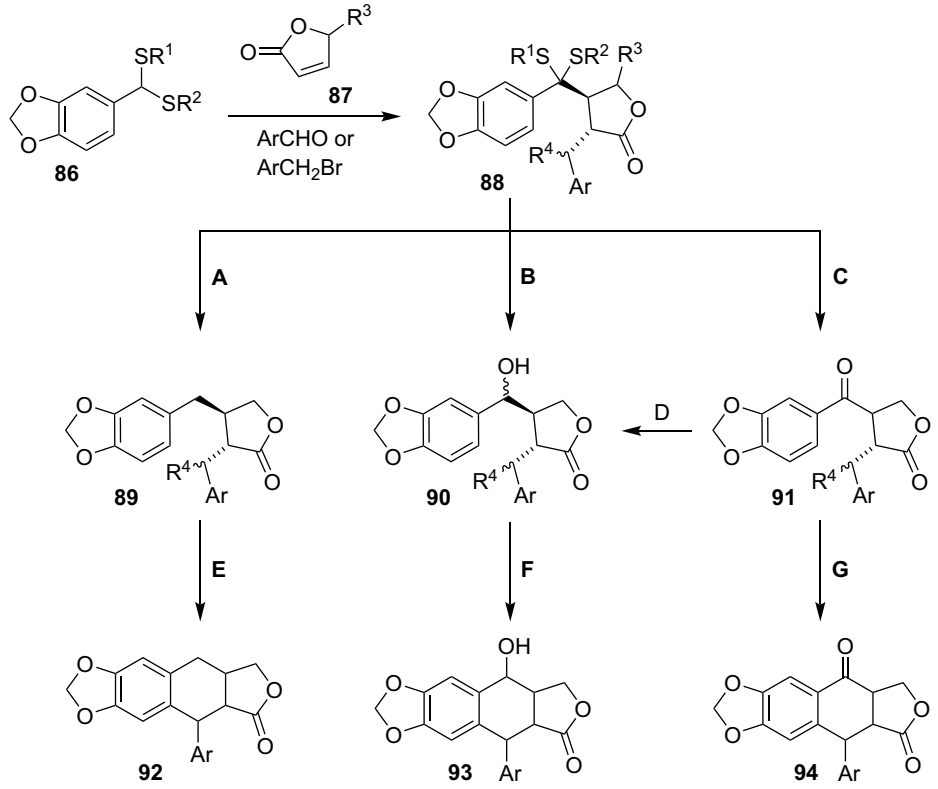
Starting from piperonal (**20**), the general strategy is that described in all the proposals of **Scheme 15** [61]. The carbonyl of piperonal (position 4) is activated as a nucleophile (**86**), which acts as a Michael donor with α,ß-unsaturated furan-2-one (**87**) which can be substituted with a chiral auxiliary in the γ position (R^3). Once the



Scheme 13. Intramolecular Diels-Alder reactions using benzocyclobutanes as diene precursors



Scheme 14. The intramolecular Diels-Alder cycloaddition using prolinol derivatives as a chiral auxiliary



Scheme 15. The general scheme of the conjugate addition method for the synthesis of aryl-tetralin lignans

1,4-addition is made, the corresponding enolate acts as a nucleophile for the aldol addition with an aryl aldehyde or a benzyl halide that already contains the corresponding *E* ring. Thus, the generic product of this transformation is a system of two phenylpropanoid units (**88**, similar to **3**) bonded by their carbons 8 and 8' (positions 3 and 2 of the tetralin lignan, respectively). This system has the dithiane group in position 4, while in position 1 it may have a hydroxyl group (R^4), depending on whether there is the aldol addition or the nucleophilic substitution.

The subsequent transformation consists of the release of the dithian group to generate a methylene (**89**, *Route A*), a methine-hydroxyl group (**90**, *Route B*) or a keto group (**91**, *Route C*) in position 4. The ring closure is carried out *via* the nucleophilic substitution from position 6 to 1 to generate the analogs of deoxypodophyllotoxin (**92**), podophyllotoxin (**93**), and podophyllotoxone (**94**).

ISSN 2308-8303 (Print) / 2518-1548 (Online)

The first two examples of this methodology were the works by *Ziegler* [62] and *González* [60, 63] (**Scheme 16**) where through dithiolanes (**86a**) the hydroxyl-lignans **88a** and **88b** were obtained, their ring *C* closure was reported to obtain the corresponding epimers: epipodophyllotoxin (**12**), picropodophyllotoxin (**13**), podophyllotoxanes (**94a**–**c**). In the 1970s, *Ziegler* provided evidence to conclude that only 1,3-dithyan nucleophiles could carry out the corresponding Michael addition; however, years later *Iwasaki* and *Ward* improved the use of 1,3-diketones or α-cyanoesters (*see* **Schemes 22**, **23** and **24**). For his part, *Ward* [64] used this same methodology from thiophenylacetals (**86b**) when constructing epimeric derivatives of podophyllotoxin **95**, from ketone **91a**.

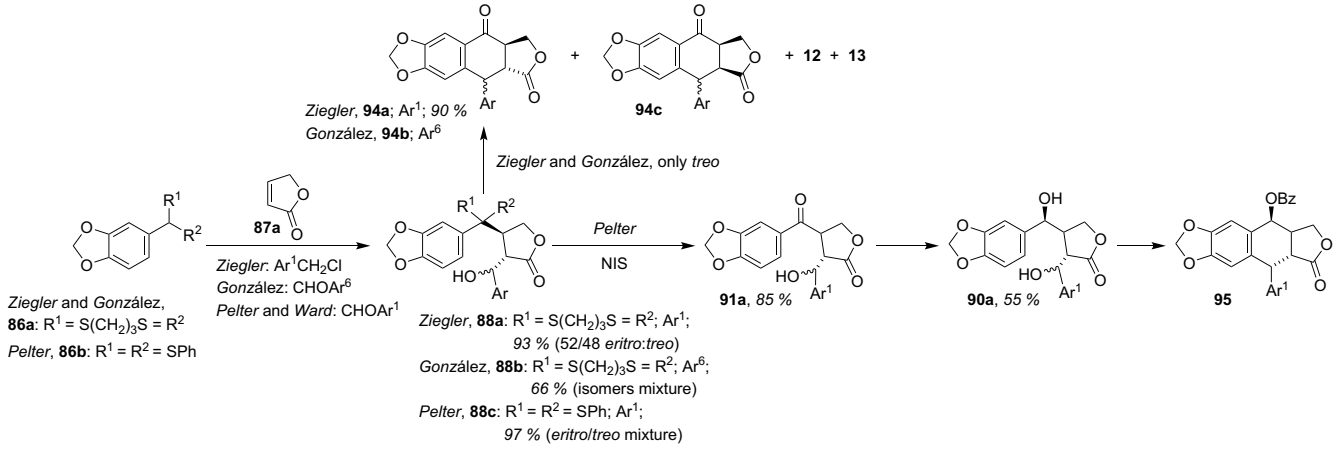
Later *Ward* also showed the option of employing a single thioether substituent (**86d,e**) to obtain analogs of desoxypodophyllotoxin (**92a**) and epipodophyllotoxin (**93a**) (**Scheme 17**).

In the early 1990s, *Kutney* [65] made two outstanding contributions to the synthesis of intermediates similar to **88** lacking ring *A*. The first was the use of benzyl halides as a source of ring *E* (**Scheme 18**; **88f** and **88g**); intermediates **89a**, **89b** and *rac*-**90d** and *rac*-**90e** were obtained from them. The second contribution consisted of the latter being reacted with a peroxidase with catalytic promiscuity from *Catharanthus roseus* plant, which had already made similar ring closures. Thus, the closure of ring *C* could be achieved in intermediate **89a** to generate **92b** and (*S*)-**90e** to generate **93b**.

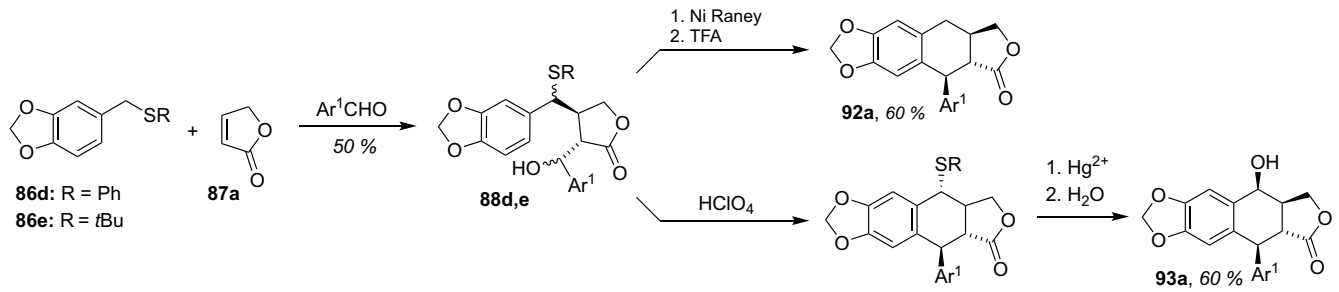
A similar method to that of **Scheme 16** was developed by *Bhat* [66], in which instead of a thioacetal, phenylsulfoxide **86h** was used as a nucleophile to subsequently follow the *Pelter*-*Ward* route (**Scheme 19**). It is noteworthy that it was possible to synthesize podophyllotoxin (**1**) in just a few steps of synthesis.

One of the strategies to control the diasteroselectivity of type **88** compounds was to incorporate a menthyl group (in its two configurations) as a chiral auxiliary in furanone **87** (**87b**) (**Scheme 20**) and react it with the corresponding anions of thioketals (**86i**) [67–70] and dithiolanes (**86j**) [71].

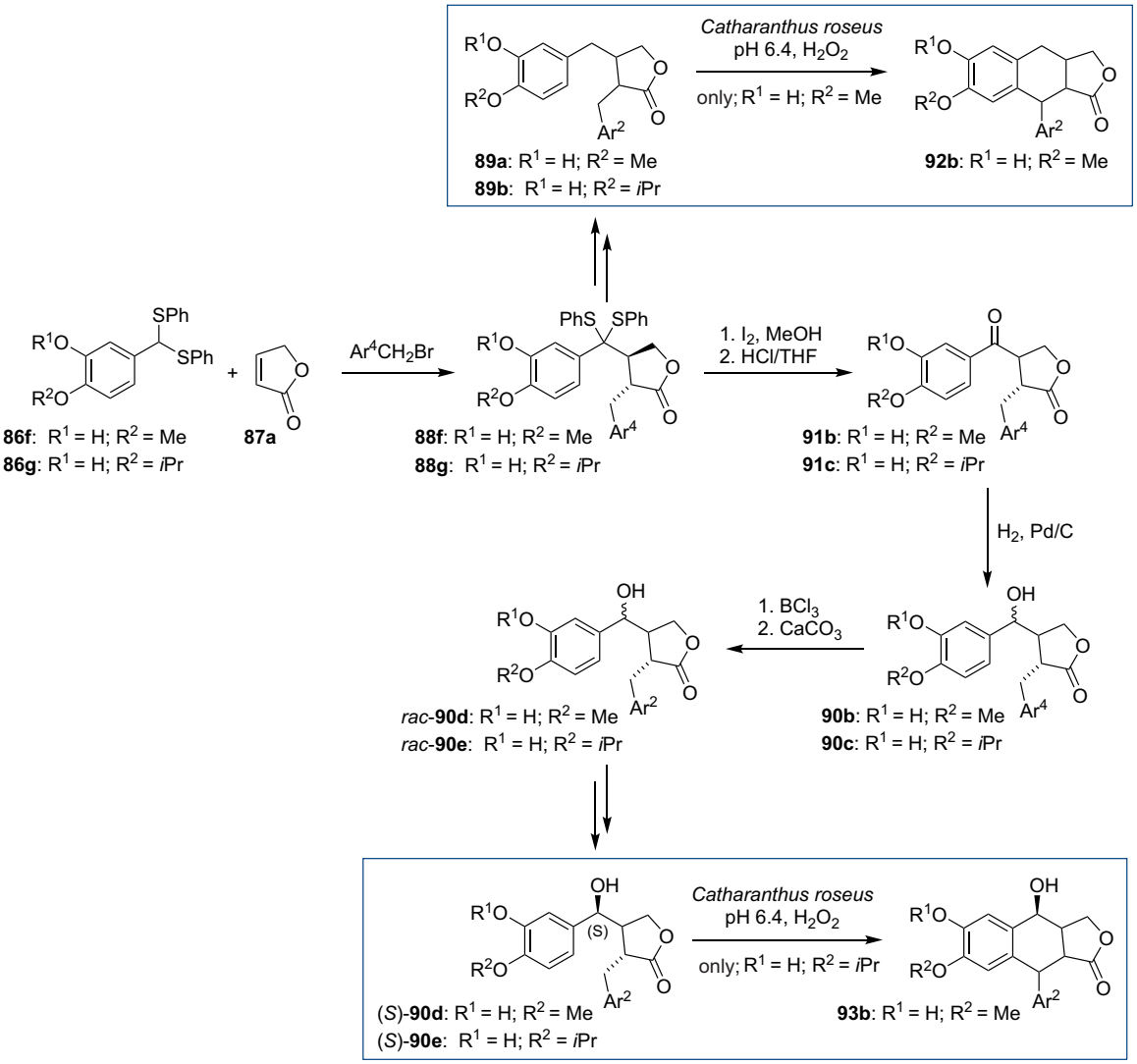
The idea of including chiral auxiliaries in type **87** furanones was originally proposed by *Koga* and his collaborators [25, 72]. In the similar synthesis to those previously explained, dithiane **96** (ring *E* activated as dithiane) was used to carry out the Michael type addition on lactone **87c** and obtain the activated intermediate **97**, a phenylpropanoid system with rings *D* and *E* joined through positions 1 and 2 (**Scheme 21**). In this case, rings *A* and *B* are integrated as piperonyl bromide through a nucleophilic substitution to



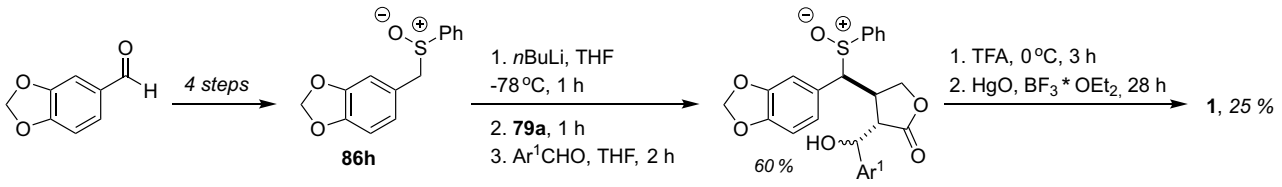
Scheme 16. First examples of the conjugate addition as a synthesis method of aryltetralin lignans



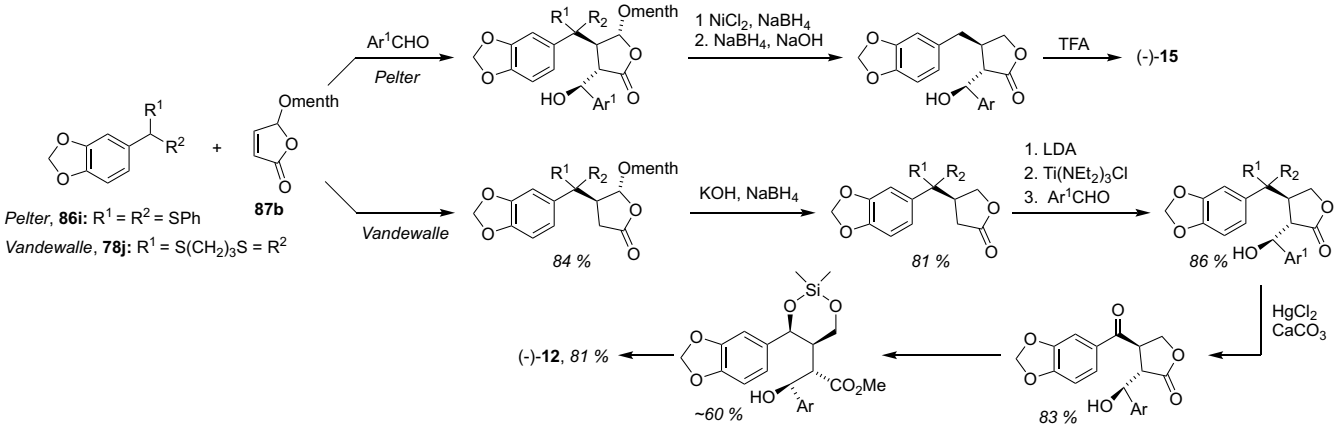
Scheme 17. The synthesis of deoxypodophyllotoxin (**85**) and epipodophyllotoxin (**86**) from thioethers derived from piperonal



Scheme 18. The closure of C ring using the enzymatic catalysis with peroxidase from *Catharantus roseus*

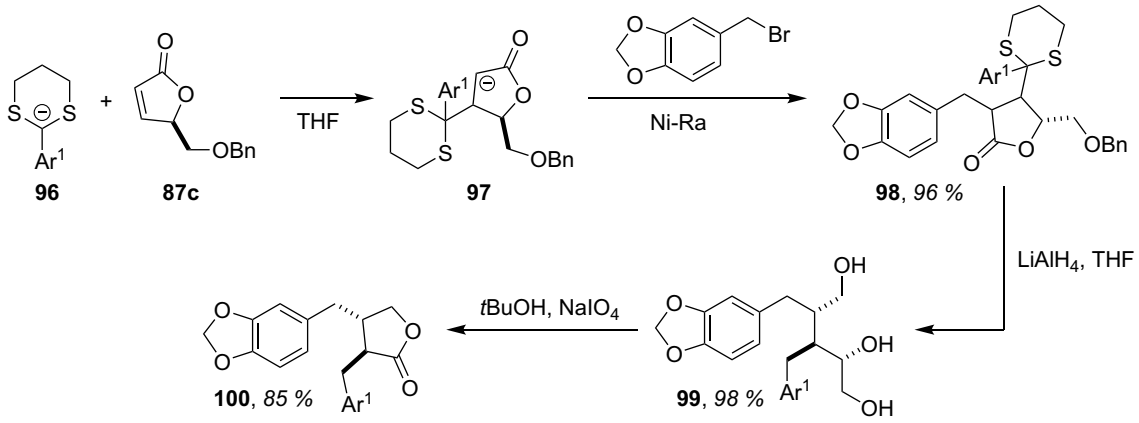


Scheme 19. The synthesis of podophyllotoxin using phenylsulfoxides

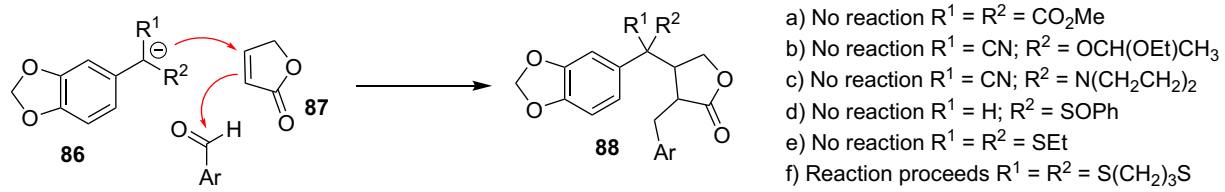


Scheme 20. The conjugate addition using chiral menthyl auxiliaries in furanones

ISSN 2308-8303 (Print) / 2518-1548 (Online)



Scheme 21. The first inclusion of chiral auxiliaries in the conjugated addition for the synthesis of lignans



Scheme 22. Proposals for activation of position 4 in the α-carbon form of carbonyls and thioacetals

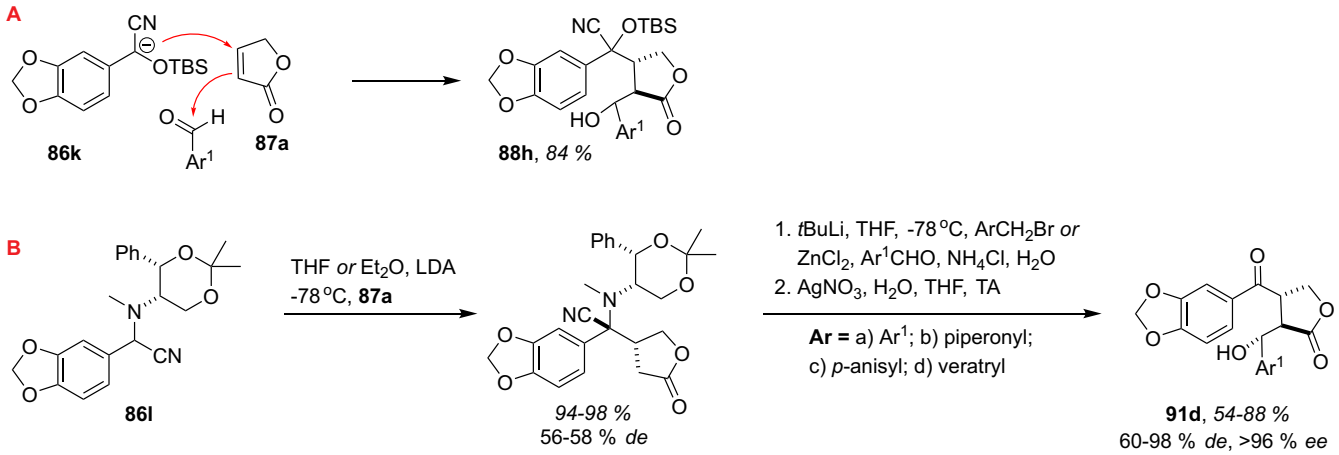
obtain **98**. The removal of the ester, benzyl and dithiane groups generated lignan **99**, which subsequent oxidation generated (+)-burseran (**100**), a direct precursor of an epimer of deoxypodophyllotoxin.

As mentioned above, *Ziegler* studied the activation of position 4 as a nucleophile by placing it in the α-position of thioacetals and carbonyl systems; however, the latter did not generate good results in the synthesis of podophyllotoxin-type lignans at the time (**Scheme 22**).

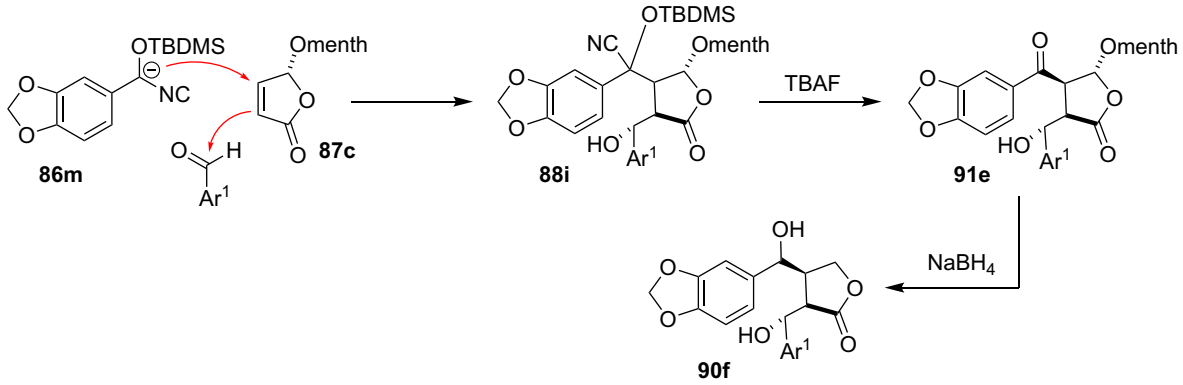
This technique was later improved by *Iwasaki* [73] and *Ward* [74] by implementing TBS-type protecting groups in position 4 (**86k**) and thus obtaining **88h**-type compounds (**Scheme 23**, *A*). The second stage of this methodology was proposed by *Enders* [75, 76] and his collaborators by incorporating secondary amines as chiral auxiliaries (**86l**), preserving the nitrile group (**Scheme 23**, *B*). The Michael-type addition of the corresponding nucleophile proceeded with diasteromeric excesses of up to 98%. The subsequent removal of the auxiliary and the aldol condensation with different aldehydes reached 88% yield and up to 96% enantiomeric excess for compound **91d**.

The use of menthol as a chiral auxiliary has also been implemented in this methodology. *Storer* [77] reacted α-anion **86m** with ketone **87b** to obtain **88i**, which could be oxidized to ketone **91e** and reduced to alcohol **90f** (**Scheme 24**).

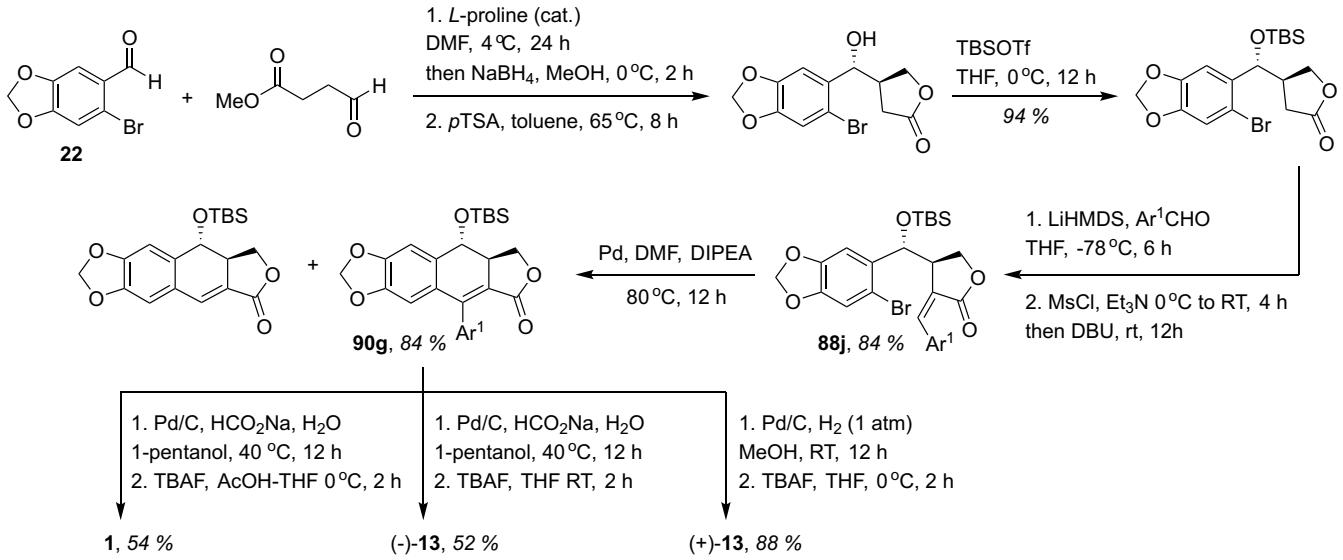
Recently, *Hazra* [78] provided a new methodology for the formation of type **88** (**88j**) intermediates through aldol-type reactions with bromopiperonal (**22**) and *in situ* formation of *D* ring (**Scheme 25**). This compound was cyclized to form intermediate **90g** from which it was possible



Scheme 23. The activation of position 4 through α anions of nitriles



Scheme 24. The use of menthol as a chiral auxiliary in the conjugate addition of alpha anions to nitrile

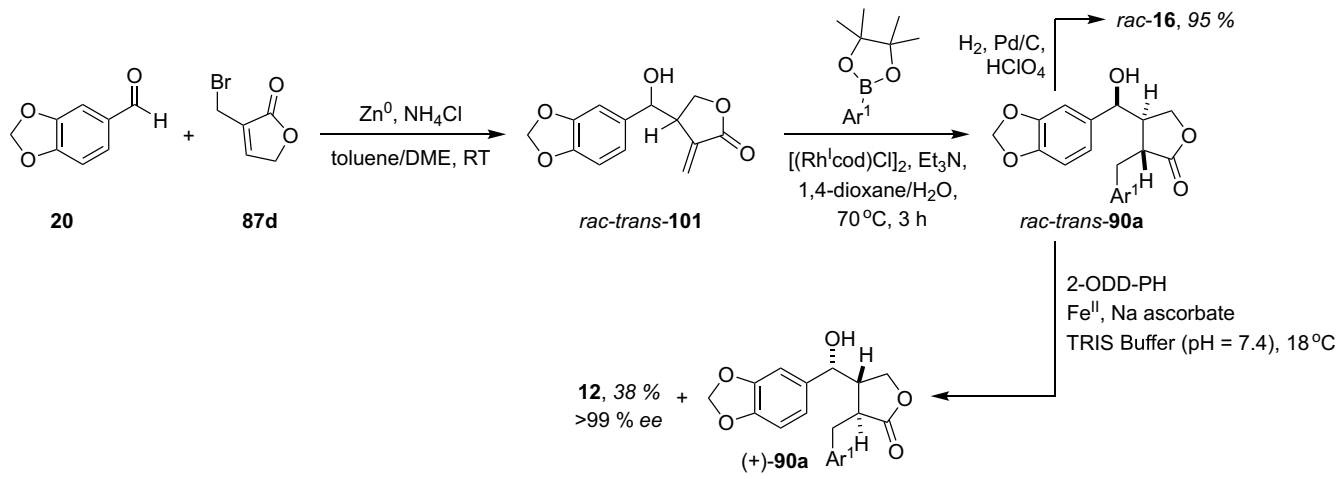


Scheme 25. The alternative in the synthesis of lignans by the conjugate addition

to differentially obtain podophyllotoxin (**1**) and two of its epimers (–)-**13** and (+)-**13**.

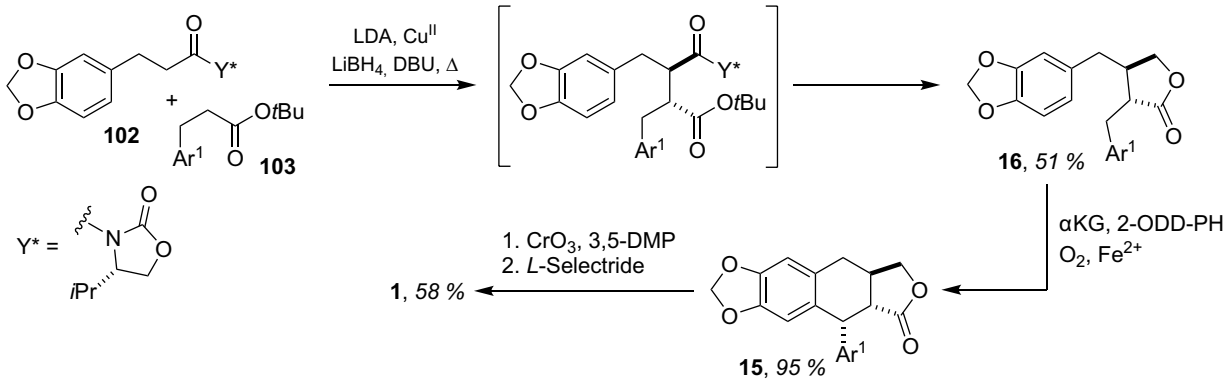
The synthesis of podophyllotoxin and analogs reported by *Fuchs* [79] could also be included in the conjugate additions. The reaction of piperonal with bromomethylfuranone (**87d**) yields *rac-trans*-**101**, which after the Michael type addition generates *rac-trans*-**90a** (hydroxyyatein) from which racemic yatein **16** could be formed (**Scheme 26**). It highlights the integration of a biocatalytic protocol using the enzyme 2-ODD-PH to carry out the formation of cycle *C* and the stereoselective obtaining of hydroxyyatein (+)-**90a**.

Renata [80] also used the enzyme 2-ODD-PH in the cyclization of yatein (**16**), it was prepared *via* cross-heterocoupling of enolates of compounds **102**



Scheme 26. Obtaining hydroxyyatein and epipodophyllotoxin *via* an alternate conjugated addition from piperonal

ISSN 2308-8303 (Print) / 2518-1548 (Online)



Scheme 27. The synthesis of yatein, deoxypodophyllotoxin and podophyllotoxin implementing the enzymatic cyclization and cross-heterocoupling

and **103** from which dehydroxypodophyllotoxin (**15**) was subsequently obtained (**Scheme 27**).

A strategy that shares the same reasoning as the conjugate additions described so far is the *Bach*'s [81] strategy, in which the formation of ring *C* is the critical step in the podophyllotoxin synthesis. Starting from (3,4,5-trimethoxy)-benzaldehyde and vinylfuranone **104**, rings *D* and *E* were incorporated *via* the aldol addition to subsequently incorporate the piperonyl group *via* the Friedel-Crafts alkylation to obtain intermediate **105**. With the formation of the corresponding ring *C* a 4-exovinylpodophyllotoxin (**106**) could be generated, its reduction generated podophyllotoxin (**1**) (**Scheme 28**).

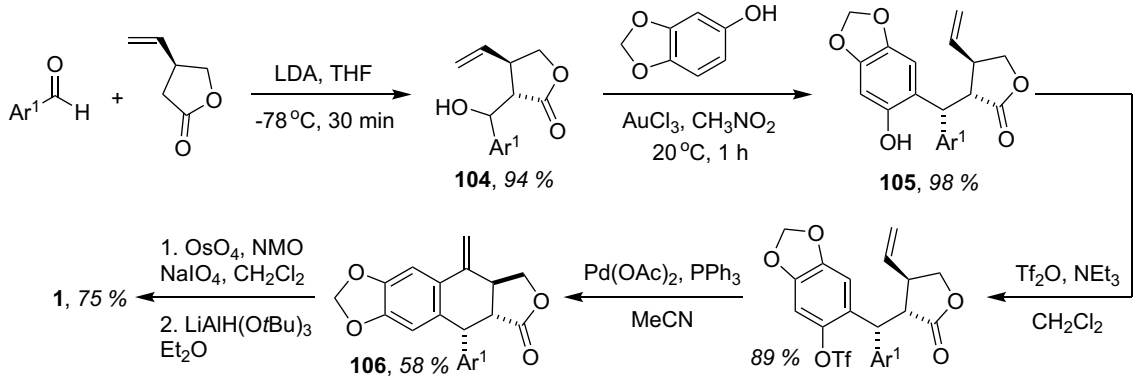
The synthesis of ring *D*

The synthesis of ring *D* in aryl-tetralin lignans of the podophyllotoxin type and their structural analogs is a poorly differentiated topic in discussions of the total synthesis of these compounds. The main methods consider that the most critical transformations are those that allow the synthesis of ring *C* with the proper configuration of its four tetrahedral carbons and that the synthesis of ring *D* is usually easier to carry out, either as an intermediate or final step. Although in most methods the formation of ring *D* is relatively simple, it is worth pointing out some peculiarities in this regard.

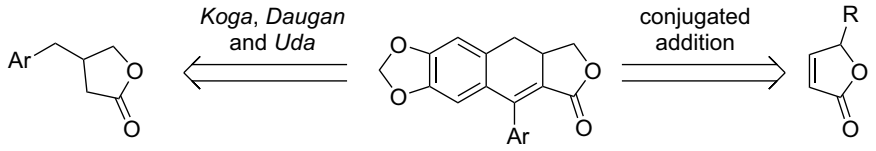
Incorporation of preformed rings

The simplest method to obtain ring *D* is its incorporation through a precursor that already contains it (**Scheme 29**). The works of *Koga*, *Daugan* and *Uda* mentioned in **Scheme 5** and the general strategy of the conjugate addition in **Scheme 12** are examples of this methodology.

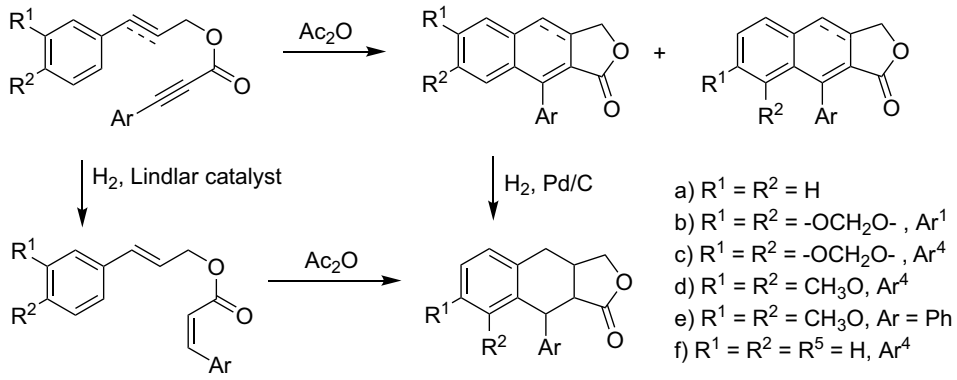
Another way to reach this ring is through the Diels-Alder type intramolecular cycloadditions proposed by *Klemm*, described in **Scheme 12**. In this strategy, the ester group, which will later be the



Scheme 28. The podophyllotoxin synthesis through a 4-exovinyl-podophyllotoxin formed *via* the Friedel-Crafts acylation



Scheme 29. The incorporation of ring *D* through precursors that already have formed it



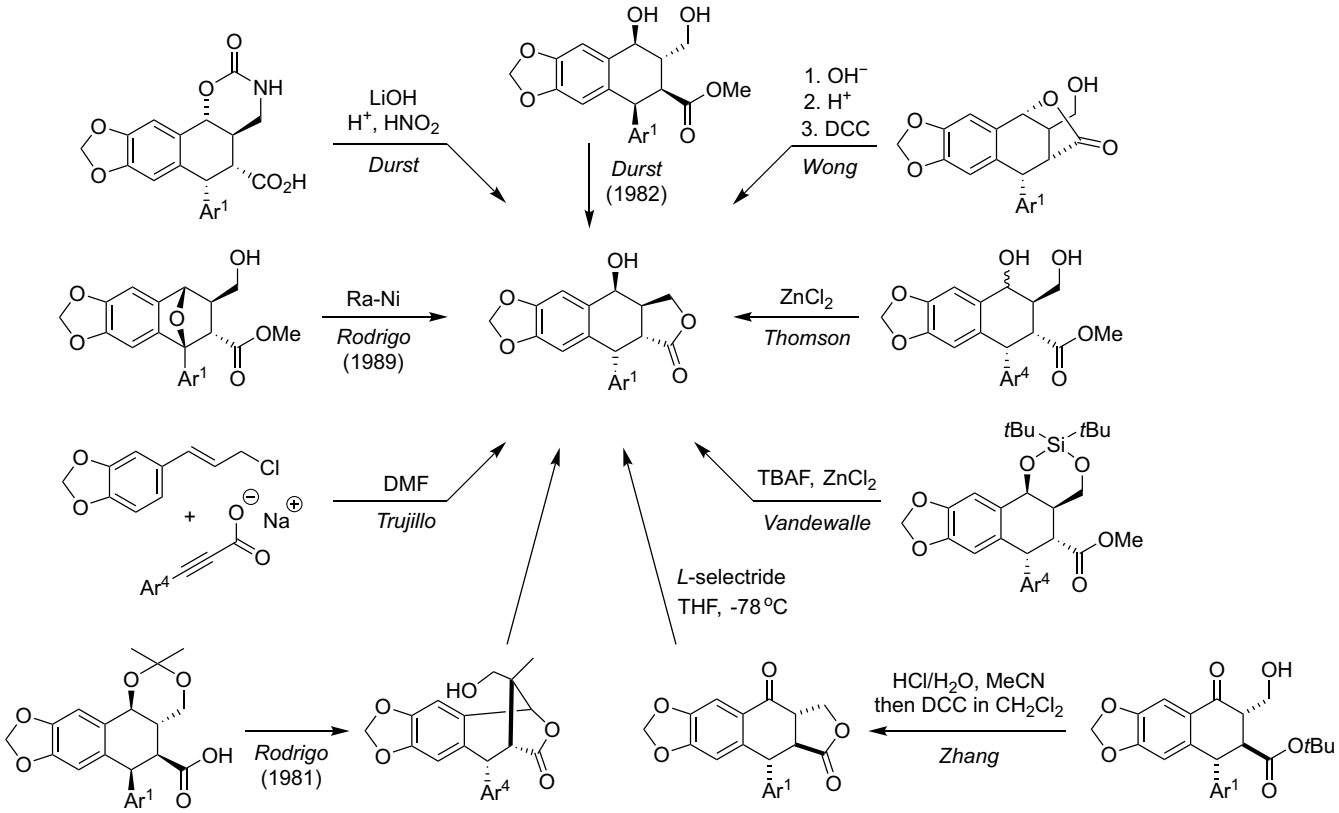
Scheme 30. The ring *D* formation by the intramolecular Diels-Alder addition

lactone, is already formed, and the cycloaddition will complete the formation of rings *C* and *D* (**Scheme 30**).

Lactonization

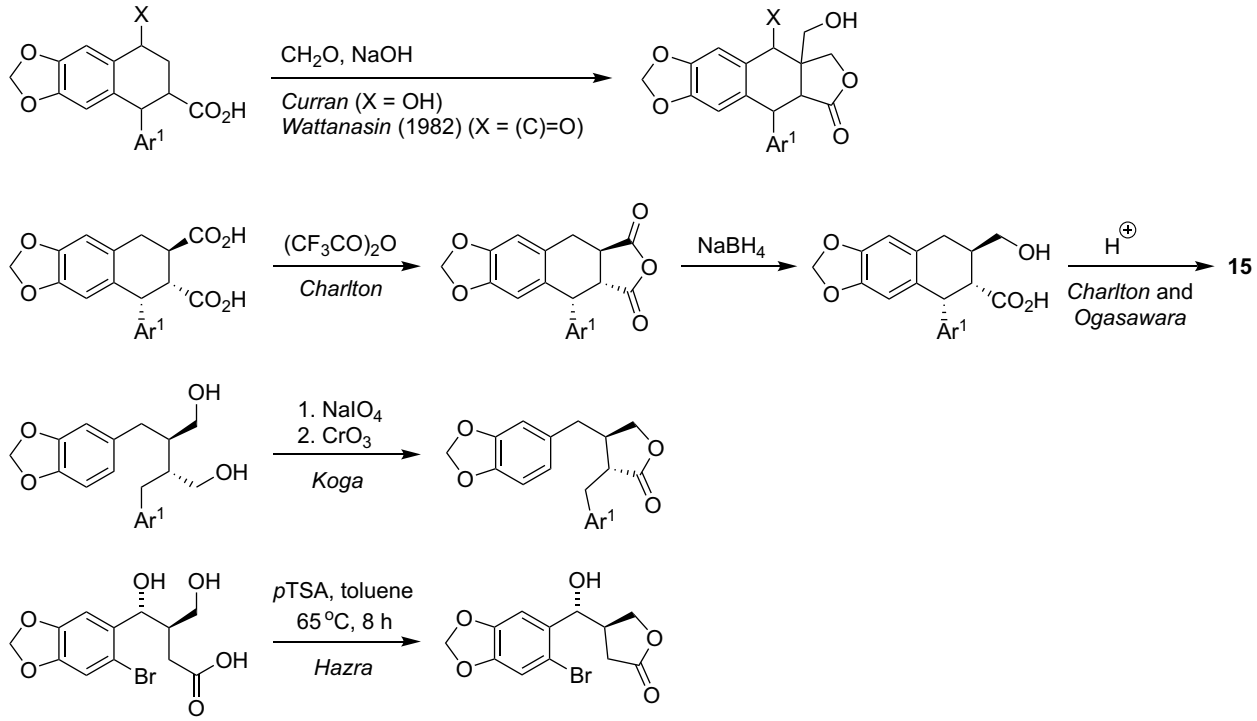
When the incorporation of the complete *D* ring is not possible, a strategy that is convenient due to its simplicity and variety of conditions is the formation of the lactone-type bond from precursors that have a hydroxymethyl group or its synthetic equivalent in position 3 and an acid derivative in position 2. Thus, we can find examples where the synthesis of ring *D* is the last step to synthesize podophyllotoxin (**Scheme 31**) or to obtain its analogs or precursors of it (**Scheme 32**). Thus, we can find the contributions of *Rodrigo*, [82, 83] *Trujillo*,[60, 62] *Curran*, [23] *Koga*, [25] *Wattanasin*, [84] *Takano*, [44] *Wong*, [85] *Durst*, [40, 56, 57] *Vandewalle*, [70] *Thomson*, [42] *Charlton*, [43] *Meyers*, [86] and *Zhang* [30, 31, 79]. It is possible to find variants where ring *D* is formed before incorporating other rings as in the case of *Hazra* [25].

Sherburn [87] reported an interesting case of the formation of ring *D*, and the incorporation of ring *E*. Starting from vinyl piperonal **27** and crotonyl-oxazolidinone **107**, the aldol reaction product **108** was obtained, its chiral auxiliary release generated **109**. The formation of ring *C* was through the metathesis to generate tetralin **110**. The key to forming rings *D* and *E* was the incorporation of a thiocarbonate group (**111**). Thus, the epimeric protein derivative of podophyllotoxin **112**

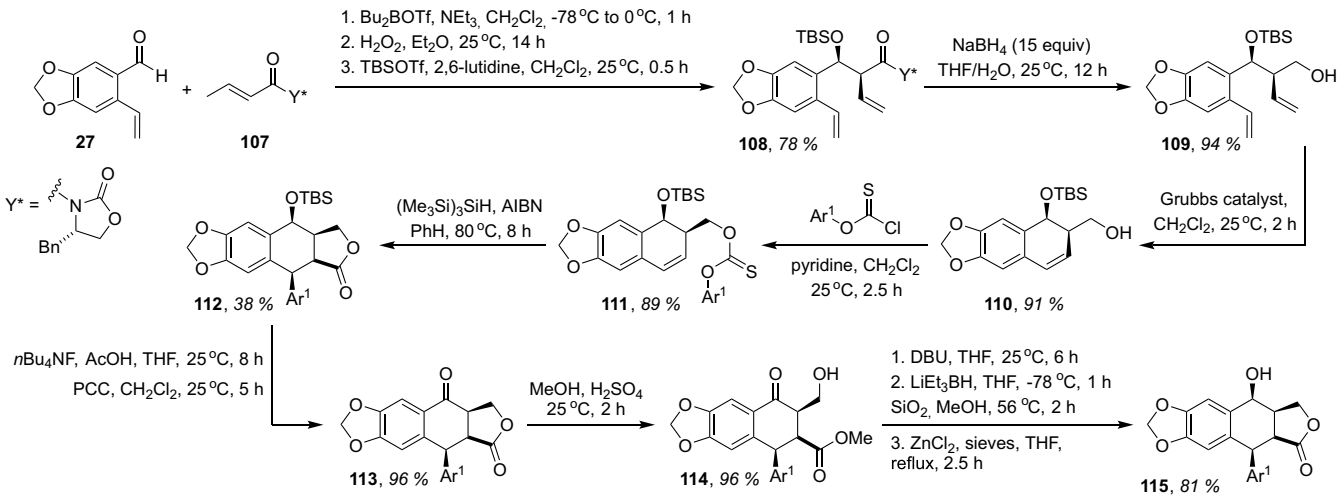


Scheme 31. The ring *D* synthesis *via* esterification to form lactones to obtain podophyllotoxin

ISSN 2308-8303 (Print) / 2518-1548 (Online)



Scheme 32. The ring *D* synthesis *via* esterification to form lactones and analogs and precursors of podophyllotoxin



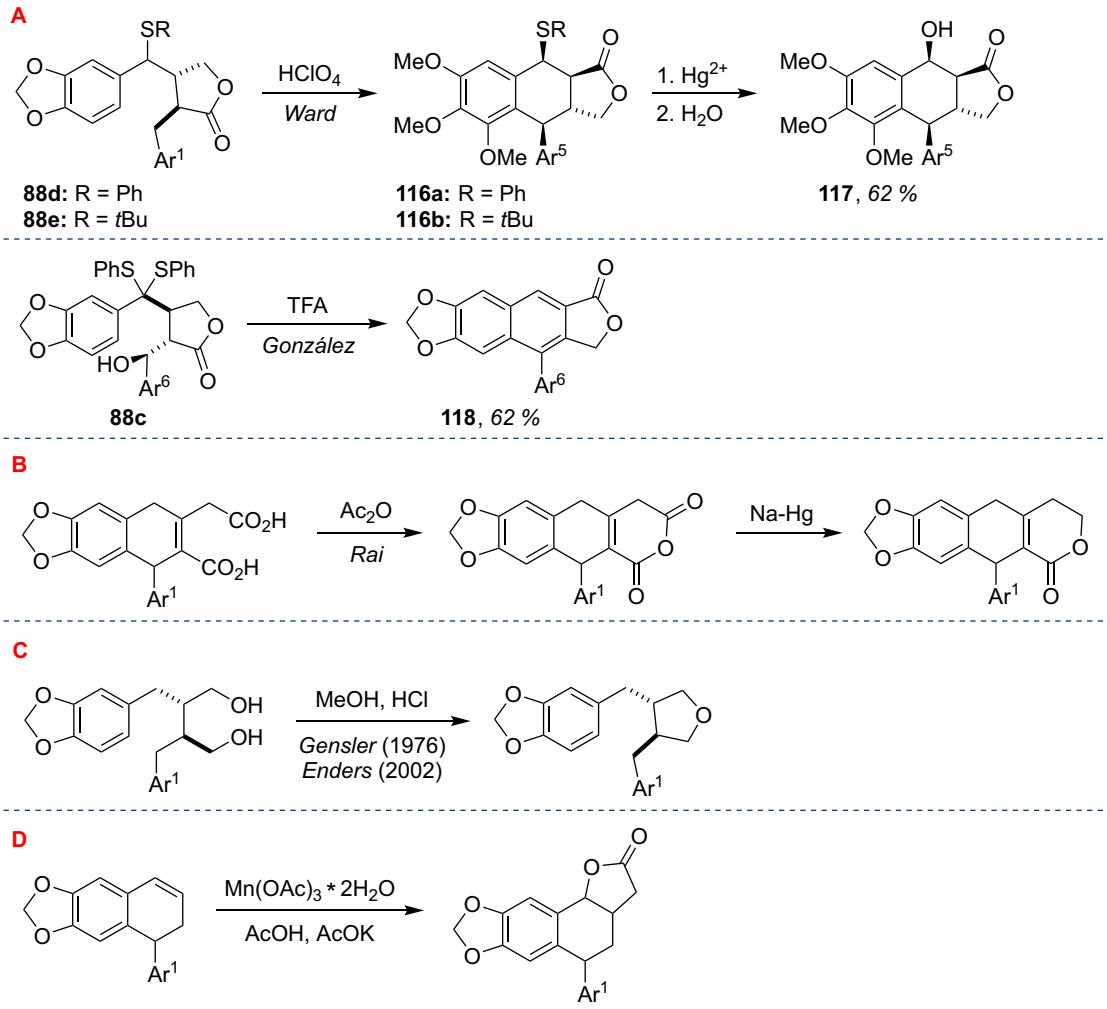
Scheme 33. The ring *E* incorporation and the ring *D* formation in the synthesis of podophyllotoxin and podophyllotoxone epimers

could be transformed into a podophyllotoxone (**113**), podophyllotoxin ester **114** and in podophyllotoxin epimer **115** (**Scheme 33**).

Within the variety of options around ring *D*, it is possible to find that analogs have been proposed with a change in the position of the lactone function (referred to in this context as retrolactone: **117** and **118**, **Scheme 34A**) [58, 59], a greater number of atoms forming the ring (**Scheme 34B**), [88] of saturated heterocycles (**Scheme 34C**), [66, 89] or in different positions (**Scheme 34D**) [90].

■ Conclusion

Taking podophyllotoxin as a natural prototype (**1**), the synthesis of aryltetralin lignans continues to be a topic of interest due to their potential as therapeutic agents. During the last seven decades, the variety and quantity of works referring to the synthesis of these compounds have been so enriched that methodological classifications have been organized and have made it easier to understand the state of progress of this area of knowledge. The present bibliographic review



Scheme 34. Structural variants in ring *D*

has proposed a new classification focused on how to synthesize and functionalize the five rings of podophyllotoxin and its structural analogs, which will give the opportunity for synthetic and pharmaceutical chemistry groups to have a guide for optimizing already existing compound synthesis, as well as proposals from other representatives of this family.

References

1. Seegers, C.; Setroikromo, R.; Quax, W. Towards Metabolic Engineering of Podophyllotoxin Production. In *Natural Products and Cancer Drug Discovery*, Farid, A. B., Ed. IntechOpen: Rijeka, 2017. https://doi.org/10.5772/67615.
2. Cheng, W.-H.; Shang, H.; Niu, C.; Zhang, Z.-H.; Zhang, L.-M.; Chen, H.; Zou, Z.-M. Synthesis and Evaluation of New Podophyllotoxin Derivatives with *in Vitro* Anticancer Activity. *Molecules* **2015**, *20*, 12266–12279. https://doi.org/10.3390/molecules200712266.
3. Gordaliza, M.; García, P. A.; Miguel del Corral, J. M.; Castro, M. A.; Gómez-Zurita, M. A. Podophyllotoxin: distribution, sources, applications and new cytotoxic derivatives. *Toxicon* **2004,** *44* (4), 441–459. https://doi.org/10.1016/j.toxicon.2004.05.008.
4. Moss, G. P. Nomenclature of Lignans and Neolignans (IUPAC Recommendations 2000). *Pure Appl. Chem.* **2000,** *72* (8), 1493–1523. https://doi.org/10.1351/pac200072081493.
5. Hande, K. R. Etoposide: four decades of development of a topoisomerase II inhibitor. *European Journal of Cancer* **1998,** *34* (10), 1514–1521. https://doi.org/10.1016/S0959-8049(98)00228-7.
6. Kaplan, I. W. Condylomata acuminata. *New Orleans Med. Surg. J*. **1942**, *94*, 388–390.
7. Guerram, M.; Jiang, Z.-Z.; Zhang, L.-Y. Podophyllotoxin, a medicinal agent of plant origin: past, present and future. *Chinese Journal of Natural Medicines* **2012,** *10* (3), 161–169. https://doi.org/10.3724/SP.J.1009.2012.00161.
8. Singh, A.; Choudhary, R.; Ganguly, S. Podophyllin in Dermatology: Revisiting a Historical Drug. *Indian Dermatol Online J.* **2022**, *24*, 167–171. https://doi.org/10.4103/idoj.idoj_225_21.
9. Fathi-karkan, S.; Arshad, R.; Rahdar, A.; Ramezani, A.; Behzadmehr, R.; Ghotekar, S.; Pandey, S. Recent advancements in the targeted delivery of etoposide nanomedicine for cancer therapy: A comprehensive review. *European Journal of Medicinal Chemistry,* **2023**, 115676
10. Guo, Q.; Jiang, E.; Recent Advances in the Application of Podophyllotoxin Derivatives to Fight Against Multidrug-Resistant Cancer Cells. *Curr Top Med Chem.* **2021**, *21*, 1712–1724. https://doi.org/10.2174/1568026621666210113163327.
11. (a) Gensler, W. J.; Gatsonis, C. D. The Podophyllotoxin—Picropodophyllin Equilibrium1,2. *J. Org. Chem.* **1966,** *31* (10), 3224–3227. https://doi.org/10.1021/jo01348a030. (b) Gensler, W. J.; Gatsonis, C. D. Synthesis of Podophyllotoxin. *J. Org. Chem.* **1966,** *31* (12), 4004–4008. https://doi.org/10.1021/jo01350a028.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

12. Medarde, M.; Ramos, A. C.; Caballero, E.; Luis López, J.; Peláez-Lamamiéde Clairac, R.; San Feliciano, A. A new approach to the synthesis of podophyllotoxin based on epimerization reactions. *Tetrahedron Lett.* **1996,** *37* (15), 2663–2666. https://doi.org/10.1016/0040-4039(96)00355-3.
13. Keller-Juslen, C.; Kuhn, M.; Von Wartburg, A.; Staehelin, H. Mitosis-inhibiting natural products. 24. Synthesis and antimitotic activity of glycosidic lignan derivatives related to podophyllotoxin. *J. Med. Chem.* **1971,** *14* (10), 936–940. https://doi.org/10.1021/jm00292a012.
14. Decembrino, D.; Raffaele, A.; Knöfel, R.; Girhard, M.; Urlacher, V. B. Synthesis of (–)–deoxypodophyllotoxin and (–)–epipodophyllotoxin via a multi-enzyme cascade in E. coli. *Microbial Cell Factories* **2021,** *20* (1), 183. https://doi.org/10.1186/s12934-021-01673-5.
15. Schultz, B. J.; Kim, S. Y.; Lau, W.; Sattely, E. S. Total Biosynthesis for Milligram-Scale Production of Etoposide Intermediates in a Plant Chassis. *J. Am. Chem. Soc.* **2019,** *141* (49), 19231–19235. https://doi.org/10.1021/jacs.9b10717.
16. Wessig, P.; John, L.; Mertens, M. Extending the Class of [1,3]-Dioxolo[4.5-f]benzodioxole (DBD) Fluorescent Dyes. *Eur. J. Org. Chem.* **2018,** *2018* (14), 1674–1681. https://doi.org/10.1002/ejoc.201800002.
17. Preparation method of piperonal (Suzhou Homesun Pharmaceutical Co ltd). Patent CN108752310 B, Nov 6, 2018.
18. Yanagisawa, A.; Chujo, I.; Tsumuki, H.; Mohri, Sh.-i. Process for preparation of 1,3-benzodioxole-2-spiro-cycloalkane derivatives (KH Neochem Co Ltd). Patent EP1535920 A1, Jun 1, 2005.
19. Aitken, R. A. 5.6–Five-Membered Ring Systems: With O and S (Se, Te) Atoms. In *Prog. Heterocycl. Chem.*, Gribble, G. W.; Joule, J. A., Eds. Elsevier: 2020; Vol. 31, pp. 379–397. https://doi.org/10.1016/B978-0-12-819962-6.00010-5.
20. Jin, Z.; Ro, D.-K.; Kim, S.-U.; Kwon, M. Piperonal synthase from black pepper (Piper nigrum) synthesizes a phenolic aroma compound, piperonal, as a CoA-independent catalysis. *Applied Biological Chemistry* **2022,** *65* (1), 20. https://doi.org/10.1186/s13765-022-00691-0.
21. Lima, L. M. Safrole and the Versatility of a Natural Biophore. *Rev. Virtual Quim.* **2015**, *7* (2), 495–538. https://doi.org/10.5935/1984-6835.20150023.
22. Tentori, F.; Brenna, E.; Ferrari, C.; Gatti, F. G.; Ghezzi, M. C.; Parmeggiani, F. Chemo-enzymatic oxidative cleavage of isosafrole for the synthesis of piperonal. *Reaction Chemistry & Engineering* **2021,** *6* (9), 1591–1600. https://doi.org/10.1039/D1RE00173F.
23. Tanigawa, H.; Oka, K. Process for the production of sesamol formic acid ester and sesamol (Daicel Corp). Patent DE60101020 T2, Jun 24, 2004.
24. Robinson, G. M. XXX.—A reaction of homopiperonyl and of homoveratryl alcohols. *Journal of the Chemical Society, Transactions* **1915,** *107* (0), 267–276. https://doi.org/10.1039/CT9150700267.
25. Kende, A. S.; Liebeskind, L. S.; Mills, J. E.; Rutledge, P. S.; Curran, D. P. Oxidative aryl-benzyl coupling. A biomimetic entry to podophyllin lignan lactones. *J. Am. Chem. Soc.* **1977,** *99* (21), 7082–7083. https://doi.org/10.1021/ja00463a062.
26. Brown, E.; Daugan, A. An easy preparation of (–) and (+)-β-piperonyl-γ-butyrolactones, key-intermediates for the synthesis of optically active lignans. *Tetrahedron Lett.* **1985,** *26* (33), 3997–3998. https://doi.org/10.1016/S0040-4039(00)98707-0.
27. Tomioka, K.; Mizuguchi, H.; Koga, K. Studies directed towards the asymmetric total synthesis of antileukemic lignan lactones. Synthesis of (–)-podorhizon. *Tetrahedron Lett.* **1978,** *19* (47), 4687–4690. https://doi.org/10.1016/S0040-4039(01)85705-1.
28. Kosugi, H.; Tagami, K.; Takahashi, A.; Kanna, H.; Uda, H. Highly enantiospecific synthesis of 4-alkyl and 4,5-dialkyl substituted 4,5-dihydrofuran-2(3H)-ones from optically active (E)- and (Z)-alk-1-enyl p-tolyl sulphoxides: application to the synthesis of lignan lactones. *J. Chem. Soc., Perkin Trans. 1* **1989,** 5, 935–943. https://doi.org/10.1039/P19890000935.
29. Van der Eycken, J.; De Clercq, P.; Vandewalle, M. Total synthesis of podophyllum lignans : an exploratory study. *Tetrahedron* **1986,** *42* (15), 4285–4295. https://doi.org/10.1016/S0040-4020(01)87655-9.
30. Van der Eycken, J.; De Clercq, P.; Vandewalle, M. Total synthesis of (±)-podophyllotoxin and (±)-epipodophyllotoxin. *Tetrahedron* **1986,** *42* (15), 4297–4308. https://doi.org/10.1016/S0040-4020(01)87656-0.
31. Kende, A. S.; King, M. L.; Curran, D. P. Total synthesis of (.+-.)-4'-demethyl-4-epipodophyllotoxin by insertion-cyclization. *J. Org. Chem.* **1981,** *46* (13), 2826–2828. https://doi.org/10.1021/jo00326a056.
32. Wu, Y.; Zhao, J.; Chen, J.; Pan, C.; Li, L.; Zhang, H. Enantioselective Sequential Conjugate Addition–Allylation Reactions: A Concise Total Synthesis of (+)-Podophyllotoxin. *Org. Lett.* **2009,** *11* (3), 597–600. https://doi.org/10.1021/ol8026208.
33. Wu, Y.; Zhang, H.; Zhao, Y.; Zhao, J.; Chen, J.; Li, L. A New and Efficient Strategy for the Synthesis of Podophyllotoxin and Its Analogues. *Org. Lett.* **2007,** *9* (7), 1199–1202. https://doi.org/10.1021/ol0630954.
34. Ward, R. S. Synthesis of Podophyllotoxin and Related Compounds. *Synthesis* **1992,** *1992* (08), 719–730. https://doi.org/10.1055/s-1992-26207.
35. Peterson, J. R.; Do, H. D.; Rogers, R. D. Anticancer Agent Development; 6.1 Application of the Heterocycle Annulation-Rearrangement Strategy in the Synthesis of a Podophyllotoxin Precursor. *Synthesis* **1991,** *1991* (04), 275–277. https://doi.org/10.1055/s-1991-26444.
36. Murphy, W. S.; Wattanasin, S. An improved route to an intermediate in podophyllotoxin synthesis. *J. Chem. Soc., Chem. Commun.* **1980,** 6, 262–263. https://doi.org/10.1039/C39800000262.
37. Vyas, D. M.; Skonezny, P. M.; Jenks, T. A.; Doyle, T. W. Total synthesis of (±) epipodophyllotoxin via a (3 + 2)-cycloaddition strategy. *Tetrahedron Lett.* **1986,** *27* (27), 3099–3102. https://doi.org/10.1016/S0040-4039(00)84725-5.
38. Kende, A. S.; Liebeskind, L. S. Total synthesis of (±)-steganacin. *J. Am. Chem. Soc.* **1976,** *98* (1), 267–268. https://doi.org/10.1021/ja00417a060.
39. Rodrigo, R. A stereo- and regiocontrolled synthesis of Podophyllum lignans. *J. Org. Chem.* **1980,** *45* (22), 4538–4540. https://doi.org/10.1021/jo01310a067.
40. Berkowitz, D. B.; Maeng, J.-H.; Dantzig, A. H.; Shepard, R. L.; Norman, B. H. Chemoenzymatic and Ring E-Modular Approach to the (–)-Podophyllotoxin Skeleton. Synthesis of 3',4',5'-Tridemethoxy-(–)-podophyllotoxin. *J. Am. Chem. Soc.* **1996,** *118* (39), 9426–9427. https://doi.org/10.1021/ja961489s.
41. Glinski, M. B.; Durst, T. Synthesis of (±)-epiisopodophyllotoxin. *Can. J. Chem.* **1983,** *61* (3), 573–575. https://doi.org/10.1139/v83-101.
42. Jones, D. W.; Thompson, A. M. Synthesis of podophyllum lignans via an isolable o-quinonoid pyrone. *J. Chem. Soc., Chem. Commun.* **1987,** 23, 1797–1798. https://doi.org/10.1039/C39870001797.
43. Jones, D. W.; Thompson, A. M. Synthesis of podophyllum lignans via an isolable o-quinonoid pyrone. *J. Chem. Soc., Perkin Trans. 1* **1993,** 21, 2533–2540. https://doi.org/10.1039/P19930002533.
44. Bogucki, D. E.; Charlton, J. L. An Asymmetric Synthesis of (-)-Deoxypodophyllotoxin. *J. Org. Chem.* **1995,** *60* (3), 588–593. https://doi.org/10.1021/jo00108a021.
45. Takano, S.; Hatakeyama, S.; Ogasawara, K. Alternative synthesis of (±)-eburunamenine via cleavage of a cyclic dithioacetal of an α-oxothione. *J. Chem. Soc., Chem. Commun.* **1977,** 2, 68. https://doi.org/10.1039/C39770000068.

46. Choy, W. An enantioselective total synthesis of epiisopodophyllotoxin. *Tetrahedron* **1990,** *46* (7), 2281–2286. https://doi.org/10.1016/S0040-4020(01)82009-3.
47. Ting, C. P.; Maimone, T. J. C—H Bond Arylation in the Synthesis of Aryltetralin Lignans: A Short Total Synthesis of Podophyllotoxin. *Angew. Chem. Int. Ed.* **2014,** *53* (12), 3115–3119. https://doi.org/10.1002/anie.201311112.
48. Ting, C. P.; Tschanen, E.; Jang, E.; Maimone, T. J. Total synthesis of podophyllotoxin and select analog designs via C–H activation. *Tetrahedron* **2019,** *75* (24), 3299–3308. https://doi.org/10.1016/j.tet.2019.04.052.
49. Klemm, L. H.; Gopinath, K. W. An intramolecular diels-alder reaction. A simple synthesis of γ-apopicropodophyllin. *Tetrahedron Lett.* **1963,** *4* (19), 1243–1245. https://doi.org/10.1016/S0040-4039(01)90810-X.
50. Klemm, L. H.; Gopinath, K. W.; Hsu Lee, D.; Kelly, F. W.; Trod, E.; McGuire, T. M. The intramolecular diels-alder reaction as a route to synthetic lignan lactones. *Tetrahedron* **1966,** *22* (6), 1797–1808. https://doi.org/10.1016/S0040-4020(01)82253-5.
51. Klemm, L. H.; Lee, D. H.; Gopinath, K. W.; Klopfenstein, C. E. Intramolecular Diels—Alder Reactions. III. Cyclizations of trans-Cinnamyl and Phenylpropargyl Phenylpropiolates1a. *J. Org. Chem.* **1966,** *31* (7), 2376–2380. https://doi.org/10.1021/jo01345a070.
52. Klemm, L. H.; Olson, D. R.; White, D. V. Intramolecular Diels-Alder reactions. VII. Electroreduction of .alpha.,.beta.-unsaturated esters. I. Synthesis of rac-deoxypicropodophyllin by intramolecular Diels-Alder reaction plus trans addition of hydrogen. *J. Org. Chem.* **1971,** *36* (24), 3740–3743. https://doi.org/10.1021/jo00823a017.
53. Saavedra, D. I.; Rencher, B. D.; Kwon, D.-H.; Smith, S. J.; Ess, D. H.; Andrus, M. B. Synthesis and Computational Studies Demonstrate the Utility of an Intramolecular Styryl Diels–Alder Reaction and Di-t-butylhydroxytoluene Assisted [1,3]-Shift to Construct Anticancer dl-Deoxypodophyllotoxin. *J. Org. Chem.* **2018,** *83* (4), 2018–2026. https://doi.org/10.1021/acs.joc.7b02957.
54. Klemm, L. H.; Gopinath, K. W.; Karaboyas, G. C.; Capp, G. L.; Hsu Lee, D. Syntheses and spectral studies of some dienic and enynic esters. *Tetrahedron* **1964,** *20* (4), 871–876. https://doi.org/10.1016/S0040-4020(01)98419-4.
55. Kocsis, L. S.; Brummond, K. M. Intramolecular Dehydro-Diels–Alder Reaction Affords Selective Entry to Arylnaphthalene or Aryldihydronaphthalene Lignans. *Org. Lett.* **2014,** *16* (16), 4158–4161. https://doi.org/10.1021/ol501853y.
56. Park, J.-E.; Lee, J.; Seo, S.-Y.; Shin, D. Regioselective route for arylnaphthalene lactones: convenient synthesis of taiwanin C, justicidin E, and daurinol. *Tetrahedron Lett.* **2014,** *55* (4), 818–820. https://doi.org/10.1016/j.tetlet.2013.12.014.
57. Macdonald, D. I.; Durst, T. A highly stereoselective Diels-Alder based synthesis of (±)-podophyllotoxin. *J. Org. Chem.* **1986,** *51* (24), 4749–4750. https://doi.org/10.1021/jo00374a056.
58. Macdonald, D. I.; Durst, T. A highly stereoselective synthesis of podophyllotoxin and analogues based on an intramolecular Diels-Alder reaction. *J. Org. Chem.* **1988,** *53* (16), 3663–3669. https://doi.org/10.1021/jo00251a003.
59. Jung, M. E.; Lam, P. Y. S.; Mansuri, M. M.; Speltz, L. M. Stereoselective synthesis of an analog of podophyllotoxin by an intramolecular Diels-Alder reaction. *J. Org. Chem.* **1985,** *50* (7), 1087–1105. https://doi.org/10.1021/jo00207a034.
60. Lisiecki, K.; Krawczyk, K. K.; Roszkowski, P.; Maurin, J. K.; Czarnocki, Z. Formal synthesis of (–)-podophyllotoxin through the photocyclization of an axially chiral 3,4-bisbenzylidene succinate amide ester – a flow photochemistry approach. *Org. Biomol. Chem.* **2016,** *14* (2), 460–469. https://doi.org/10.1039/C5OB01844G.
61. González, A. G.; de la Rosa, R.; Trujillo, J. M. Synthesis of new aryltetralin lignans. *Tetrahedron* **1986,** *42* (14), 3899–3904. https://doi.org/10.1016/S0040-4020(01)87544-X.
62. Ziegler, F. E.; Schwartz, J. A. Synthetic studies on lignan lactones: aryl dithiane route to (±)-podorhizol and (±)-isopodophyllotoxone and approaches to the stegane skeleton. *J. Org. Chem.* **1978,** *43* (5), 985–991. https://doi.org/10.1021/jo00399a040.
63. González, A. G.; Pérez, J. P.; Trujillo, J. M. Synthesis of two arylnaphthalene lignans. *Tetrahedron* **1978,** *34* (7), 1011–1013. https://doi.org/10.1016/0040-4020(78)88156-3.
64. Pelter, A.; Ward, R. S.; Pritchard, M. C.; Kay, I. T. Synthesis of lignans related to the podophyllotoxin series. *J. Chem. Soc., Perkin Trans. 1* **1988,** 6, 1603–1613. https://doi.org/10.1039/P19880001603.
65. Kutney, J. P. Plant Cell Cultures and Synthetic Chemistry—Routes to Clinically Important Compounds. In *Phytochemical Potential of Tropical Plants*, Downum, K. R.; Romeo, J. T.; Stafford, H. A., Eds. Springer US: Boston, MA, 1993; pp 235–265. https://doi.org/10.1007/978-1-4899-1783-6_10.
66. Hadimani, S. B.; Tanpure, R. P.; Bhat, S. V. Asymmetric total synthesis of (–) podophyllotoxin. *Tetrahedron Lett.* **1996,** *37* (27), 4791–4794. https://doi.org/10.1016/0040-4039(96)00937-9.
67. Pelter, A.; Ward, R. S.; Jones, D. M.; Maddocks, P. Asymmetric synthesis of homochiral dibenzylbutyrolactone lignans by conjugate addition to a chiral butenolide. *Tetrahedron: Asymmetry* **1990,** *1* (12), 857–860. https://doi.org/10.1016/S0957-4166(00)82273-9.
68. Pelter, A.; Ward, R. S.; Jones, D. M.; Maddocks, P. Asymmetric syntheses of lignans of the dibenzylbutyrolactone, dibenzylbutanediol, aryltetraun and dibenzocyclooctadiene series. *Tetrahedron: Asymmetry* **1992,** *3* (2), 239–242. https://doi.org/10.1016/S0957-4166(00)80200-1.
69. Palter, A.; Ward, R. S.; Jones, D. M.; Maddocks, P. Asymmetric synthesis of lignans of the dibenzylbutanediol and tetrahydrodibenzocyclooctene series. *J. Chem. Soc., Perkin Trans. 1* **1993,** 21, 2631–2637. https://doi.org/10.1039/P19930002631.
70. Pelter, A.; Ward, R. S.; Jones, D. M.; Maddocks, P. Asymmetric synthesis of dibenzylbutyrolactones and aryltetralin lignan lactones by tandem conjugate addition to a chiral butenolide. *J. Chem. Soc., Perkin Trans. 1* **1993,** 21, 2621–2629. https://doi.org/10.1039/P19930002621.
71. Van Speybroeck, R.; Guo, H.; Van der Eycken, J.; Vandewalle, M. Enantioselective total synthesis of (–)-epipodophyllotoxin and (–)-podophyllotoxin. *Tetrahedron* **1991,** *47* (26), 4675–4682. https://doi.org/10.1016/S0040-4020(01)86473-5.
72. Tomioka, K.; Ishiguro, T.; Koga, K. Asymmetric total synthesis of the antileukaemic lignans (+)-trans-burseran and (–)-isostegane. *J. Chem. Soc., Chem. Commun.* **1979,** 15, 652–653. https://doi.org/10.1039/C39790000652.
73. Ogiku, T.; Yoshida, S.-i.; Kuroda, T.; Takahashi, M.; Ohmizu, H.; Iwasaki, T. Syntheses of Aryltetralin Lignans: Concise Syntheses of (±)-Isopodophyllotoxone, (±)-Picropodophyllone and Their Related Compounds. *Bull. Chem. Soc. Jpn.* **2006,** *65* (12), 3495–3497. https://doi.org/10.1246/bcsj.65.3495.
74. S. Ward, R.; Pelter, A.; Brizzi, A.; Sega, A.; Paoli, P. Synthesis of Diversely Functionalised Dibenzylbutyrolactones and Aryltetralins from Silylated Cyanohydrin Anions. *Journal of Chemical Research, Synopses* **1998,** 5, 226–227. https://doi.org/10.1039/A704399F.
75. Enders, D.; Kirchhoff, J.; Lausberg, V. Diastereo- and Enantioselective Synthesis of Lignan Building Blocks by Tandem Michael Addition/Electrophilic Substitution of Lithiated α-Amino Nitriles to Furan-2(5H)-one. *Liebigs Annalen* **1996,** *1996* (9), 1361–1366. https://doi.org/10.1002/jlac.199619960904.
76. Enders, D.; Lausberg, V.; Del Signore, G.; Berner, O. M. A General Approach to the Asymmetric Synthesis of Lignans: (-)-Methyl Piperitol, (-)-Sesamin, (-)-Aschantin, (+)-Yatein, (+)-Dihydroclusin, (+)-Burseran, and (-)-Isostegane. *Synthesis* **2002,** *2002* (04), 0515–0522. https://doi.org/10.1055/s-2002-20967.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

77. Pelter, A.; S. Ward, R.; P. Storer, N. The asymmetric synthesis of an isomer of podophyllotoxin. *Tetrahedron* **1994,** *50* (36), 10829–10838. https://doi.org/10.1016/S0040-4020(01)89274-7.
78. Hajra, S.; Garai, S.; Hazra, S. Catalytic Enantioselective Synthesis of (–)-Podophyllotoxin. *Org. Lett.* **2017,** *19* (24), 6530–6533. https://doi.org/10.1021/acs.orglett.7b03236.
79. Lazzarotto, M.; Hammerer, L.; Hetmann, M.; Borg, A.; Schmermund, L.; Steiner, L.; Hartmann, P.; Belaj, F.; Kroutil, W.; Gruber, K.; Fuchs, M. Chemoenzymatic Total Synthesis of Deoxy-, epi-, and Podophyllotoxin and a Biocatalytic Kinetic Resolution of Dibenzylbutyrolactones. *Angew. Chem. Int. Ed.* **2019,** *58* (24), 8226–8230. https://doi.org/10.1002/anie.201900926.
80. Li, J.; Zhang, X.; Renata, H. Asymmetric Chemoenzymatic Synthesis of (–)-Podophyllotoxin and Related Aryltetralin Lignans. *Angew. Chem. Int. Ed.* **2019,** *58* (34), 11657–11660. https://doi.org/10.1002/anie.201904102.
81. Stadler, D.; Bach, T. Concise Stereoselective Synthesis of (–)-Podophyllotoxin by an Intermolecular Iron(III)-Catalyzed Friedel–Crafts Alkylation. *Angew. Chem. Int. Ed.* **2008,** *47* (39), 7557–7559. https://doi.org/10.1002/anie.200802611.
82. Forsey, S. P.; Rajapaksa, D.; Taylor, N. J.; Rodrigo, R. Comprehensive synthetic route to eight diastereomeric Podophyllum lignans. *J. Org. Chem.* **1989,** *54* (18), 4280–4290. https://doi.org/10.1021/jo00279a011.
83. Rajapaksa, D.; Rodrigo, R. A stereocontrolled synthesis of antineoplastic podophyllum lignans. *J. Am. Chem. Soc.* **1981,** *103* (20), 6208–6209. https://doi.org/10.1021/ja00410a038.
84. Murphy, W. S.; Wattanasin, S. Total synthesis of (±)-picropodophyllone. *J. Chem. Soc., Perkin Trans. 1* **1982,** 0, 271–276. https://doi.org/10.1039/P19820000271.
85. Kaneko, T.; Wong, H. Total synthesis of (±) podophyllotoxin. *Tetrahedron Lett.* **1987,** *28* (5), 517–520. https://doi.org/10.1016/S0040-4039(00)95770-8.
86. Andrews, R. C.; Teague, S. J.; Meyers, A. I. Asymmetric total synthesis of (-)-podophyllotoxin. *J. Am. Chem. Soc.* **1988,** *110* (23), 7854–7858. https://doi.org/10.1021/ja00231a041.
87. Fischer, J.; Reynolds, A. J.; Sharp, L. A.; Sherburn, M. S. Radical Carboxyarylation Approach to Lignans. Total Synthesis of (–)-Arctigenin, (–)-Matairesinol, and Related Natural Products. *Org. Lett.* **2004,** *6* (9), 1345–1348. https://doi.org/10.1021/ol049878b.
88. Anjanamurthy, C.; Rai, K. M. L. Synthesis in the field of podophyllotoxin and related analogues. Part IV: Synthesis of β-apopicropodophyllin analogues with expanded lactone ring. *Current Science* **1985**, *54* (2), 67–69.
89. Gensler, W. J.; Murthy, C. D.; Trammell, M. H. Nonenolizable podophyllotoxin derivatives. *J. Med. Chem.* **1977,** *20* (5), 635–644. https://doi.org/10.1021/jm00215a004.
90. Suresh Babu, M.; Madhavu Lokanatha Rai, K. Synthesis of Podophyllotoxin and its Derivatives via NiCl2/NaBH4 Reduction of Isoxazoline Ring. *Asian J. Chem.* **2013,** *25* (17), 9555–9557. https://doi.org/10.14233/ajchem.2013.15073.

Information about the authors:
Francisco Flóres-Hernández is bachelor's degree applicant in Chemistry, Pharmacy, and Biology, University of Guadalajara (México).
Tania Isabel Zárate-López earned a bachelor's degree in chemistry, Pharmacy, and Biology at the University Colima (2020).
As a PhD student in Biotechnological Processes at the University of Guadalajara (México), she developed chemoenzymatic and friendly environmental synthetic methods for the preparation of aryl-tetralin lignans reported in the thesis "Development of a Method for Synthesis of Podophylotoxin and Related Aryl-tetralin Lignans, Implementing Chemo-enzymatic and Green Chemistry Strategies". https://orcid.org/0000-0002-1766-3682.
Marco Antonio Alcaráz-Cano earned a bachelor's degree (2021) in Molecular Design and Nano-Chemistry at the Chemical Research Center (CIQ) of the Institute for Research in Basic and Applied Sciences (IICBA) at the Autonomous University of the State of Morelos (UAEM), with a thesis «Review of Synthesis Methods for Podophyllotoxin Reported from 2000–2021» under the supervision of Dr. Jaime Escalante. He is currently a master's degree applicant in the Laboratory of Nanochemistry and Nanocarbon under the supervision of Dr. María Luisa García Betancourt at the Chemical Research Center (CIQ) – UAEM. https://orcid.org/0000-0003-1754-0751.
Jaime Escalante studied chemistry at the UNAM in Mexico City (1985), received a M.Sc. (1991) and Ph.D. (1995) from CINVESTAV-IPN, Mexico City, with a thesis on Asymmetric Synthesis of β-amino acids (supervisor E. Juaristi). Following a post-doctoral stay at the University of Illinois at Chicago, USA (with D. Crich). Later, he returned to Mexico, where he is now a Professor of Chemistry at the Chemical Research Center of Autonomous Morelos State University. He has also served as a Visiting Professor at ETH-Zurich. https://orcid.org/0000-0001-5485-0244.
José Domingo Rivera-Ramírez (*corresponding author*) received a PhD in 2015 with a dissertation on the mechanism of selectivity of lipases mediated by the polarity of solvents. From 2014 to 2018, started to work on Signa-Apotex Inc. in the R&D department. In 2018, he moved to the University of Guadalajara (México) as assistant professor. In 2020, he founded the Laboratorio de Química Farmacéutica. His current research lines are focused on the synthesis of lignans and capsaicinoids employing green methodologies and in the elucidation of promiscuous enzymatic mechanisms. https://orcid.org/0000-0003-3188-7321;
e-mail for correspondence: domingo.rivera@academicos.udg.mx.