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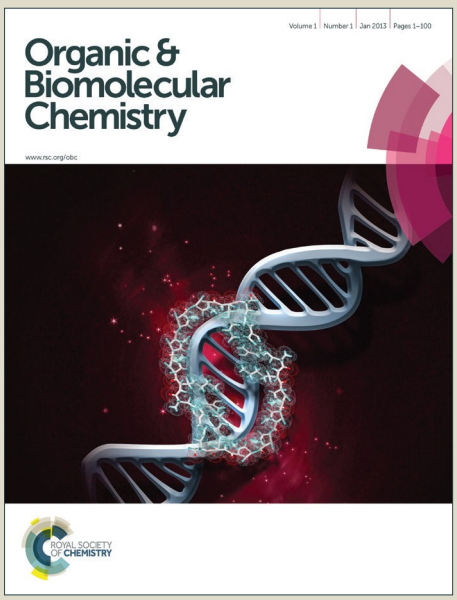

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ARTICLE

The Chemical Synthesis of Aryltetralin Glycosides

Jian-Song Sun,*[a] Hui Liu,[a] Xiao-Hong Guo,[a] and Jin-Xi Liao[a]

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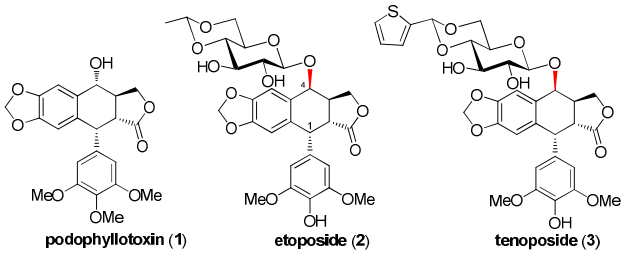
Led by the etoposide and tenoposide, the synthesis of aryltetralin glycoside has been experiencing flourishing development in the past five dacaes. Herein, a review focusing on the real sense total synthesis of aryltertalin glycoside is provided. The main body of this review is comprised by two parts, one is enantioselective synthesis of aryltetalin derivatives and the other one is the construction of the key glycosidic linkage. In each part the contents are organised based on different strategies or protocols applied in the original documents. The real sense total synthesis of aryltetralin glycoside represents the developing direction of this field, and sooner or later will replace the currently applied semi-total synthesis method with the aglycon residue acquired from natural sources directly. This account can provide a comprehensive and deep insight into the field of aryltetralin glycoside synthesis for chemists who have the intention to commit themselves to the development of aryltetralin glycoside medicines.

1 Introduction

The continued impetus for the development of highly efficient synthesis of aryltetralin glycosides stems from the discovery of two clinically used antitumor drugs derived from podophyllotoxin **1**, namely etoposide **2** and tenoposide **3** (Scheme 1).[1] As DNA topoisomerase II inhibitors, etoposide and tenoposide are currently widely applied for the treatment of many cancers, especially for small lung carcinoma and Kaposi's sarcoma.[2] In addition, many recently characterized naturally occurring aryltetralin glycoside have been demonstrated to possess diverse promising pharmaceutical applications, which will further stimulate the interests of synthetic chemists all over the world.[3] Nevertheless, the development of aryltetralin glycoside synthesis is now heavily dependent on the accessibility manner of the aryltetralin aglycons. Currently, aryltetralin derivatives such as podophyllotoxin and its congeners are solely derived from natural sources such as American Mayapple (*Podophyllum peltatum*) and related Indian species. The continuously increasing demand of aryltetralin lignans for aryltetralin glycoside making almost exhausts these natural sources, and the situation is further deteriorated by the slow growing-rate of aryltetralin lignan-containing plants. Consequently, serious ecological problems including the damage of ecological balance appear as a result of the development of aryltetralin glycoside field. Undoubtedly, chemical synthetic approaches to furnish aryltetralin enantioselectively en route to bioactive aryltetralin glycosides will be the ideal means to solve the problem encountered in aryltetralin glycoside field. At the same time, along this line a real total synthesis route starting from cheap and easily available starting materials will be established. This represents the right direction in the development of aryltetralin glycoside synthesis in the future. To service this developing trend, a review laying its emphasis on enantioselective synthesis of aryltetralin and the construction of the key glycosidic linkage of aryltetralin

[a] *The National Engineering Research Center for Carbohydrate Synthesis, Jiangxi Normal University, Nanchang 330022, China. E-mail: jssun@jxnu.edu.cn*

glycoside is highly desirable. With the intention to summarize the accomplishment achieved in arytetralin glycoside synthesis and also to complement precedented reviews, such an account is presented hererin.



Scheme 1. The structures of podophyllotoxin, etoposide and tenoposide

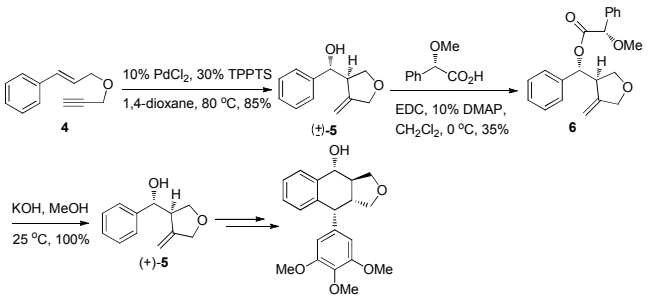
Outstanding reviews focusing on comprehensive synthesis of lignan and neolignan compounds has been presented by Ward in 1990[4] and 1999,[5] respectively. As a sequel to Ward's proceeding reviews, a review from Pan et al. laid the emphasis on both the introduction of new lignan derivatives and the new advances in chemical synthesis of lignans achieved since 1990.[6] Special attentions have been paid to the chemical synthesis of podophyllotoxin and related compounds in another instructive account of Ward,[7] which was followed by the Steel's review focusing on the synthetic advances of aryltetralin lignan.[8] In addition, the bioactivities exhibited by plant lignans were summarized by Lee and co-workers in 2005.[9] Although these precedented reviews exist, they were organized either from the whole lignan perspective, and the synthesis of all types of frequently encountered lignan were covered, or even only from aryltetralin perspective, but both enantio- and nonenantioselective approaches were included and no appropriate attention was payed to the strategies applied in the enantioselective synthesis of aryltetralin derivatives. More importantly, although it has been demonstrated that the pharmaceutical importance of aryltetralin glycoside is much higher than that of aryltetralin per se, the construction of the key glycosidic linkage is never mentioned in all preceding reviews. Considering that the real sense total synthesis route will replace the currently widely adopted semi total synthesis method to get aryltetralin glycoside, in this review the emphasis will be laid on the strategies used in enantioselective synthesis of aryltetralin derivatives and the protocols employed in glycosidic linkage construction. For clarity purpose, the main section of this account is divided into two parts, enantioselective synthesis of arytetralin and construction of the key glycosidic linkage. The former part is organized according to strategies used to achieve high enantioselective synthesis of aryltetralin, while the latter part is arranged in light of different protocols selected in glycosidic linkage construction.

2 Enantioseletive synthesis of aryltetralin

As the typical representative of aryltetralin, podophyllotoxin has been widely used in folk medicine before its antitumor activity was confirmed in 1940s. The promising pharmaceutical potential immediately triggered intense investigation toward synthetic routes led by professor Gensler.[10] Gensler's contribution in the 1950s and 1960s on synthetic, structural, and mechanistic aspects of podophyllotoxin laid firm foundation for the subsequent development of enantioselective synthesis of arytetralin derivatives which will be discussed in detail as follow.

2.1 Chiral resolution strategy

As one of the oldest means to obtain optically active compound, the resolution strategy leveraging on chiral acid esterification was introduced to unsymmetric synthesis of aryltetralin derivative by Genêt and co-workers (Scheme 2).[11] Thus, treated with water-soluble palladium catalyst prepared in situ by combination of $PdCl_2$ with water-soluble ligand TPPTS, cinnamylpropargyl ether **4** was converted to **5** diastereoselectively in a high 85% yield via carbohydroxylpalladation reaction. To obtain compound **5** in an optically active form, (S)-(+)-α-methoxyphenylacetic acid was selected as resolution reagent. Esterification of racemic **5** with chiral acid under dehydrative conditions (EDC, DMAP) furnished a pair of diastereomers which could be separated by careful silica gel chromatography, and the desired diastereomer **6** was obtained in 35% yield. Saponification under standard conditions (KOH, MeOH) afforded optically pure (+)-**5** (100%). Although (+)-**5** was not advanced to aryltetralin derivative by the authors, theoretically, it could be easily converted to arytetralin **7** via the synthetic route provided by the authors in the same paper, through which a stereoselective synthesis of aryltetralin derivative was accomplished.



Scheme 2. Enantioselective synthesis of **7** via chiral resolution

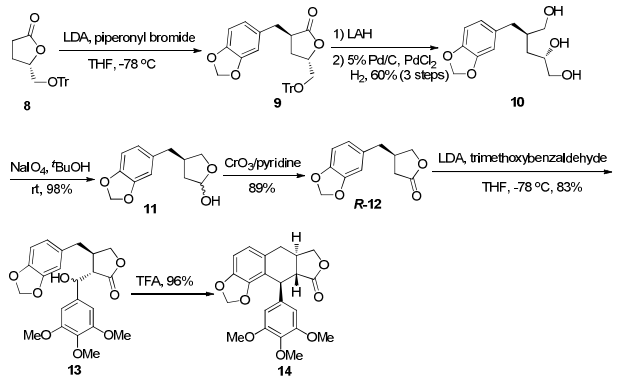
The same strategy was also exploited by Brown et al. to carry out the syntheses of a variety of of arytetralin lignans including (-)-α-conidendrin, (+)-isolariciresinol, (-)-α-dimethylretrodendrin, and (+)-isodeoxypodophyllotoxin.[12] The key chiral intermediates involved in Brown's arytetralin synthesis were obtained by optical resolution of racemic 2-benzylsuccinic acid monoester with either optical α-methylbenzylamine or chiral ephedrine via salification.

While the chiral resolution protocol is one of the most reliable means to get chiral compound in optical form, only half quantity of the desired compound could be separated

from the racemic mixture, and the processes of searching for optimal resolution reagent and separation of one diastereomer from a mixture of two diastereomers with similar polarity are quite time-consuming. Therefore, the whole efficiency of this protocol is not satisfactory.

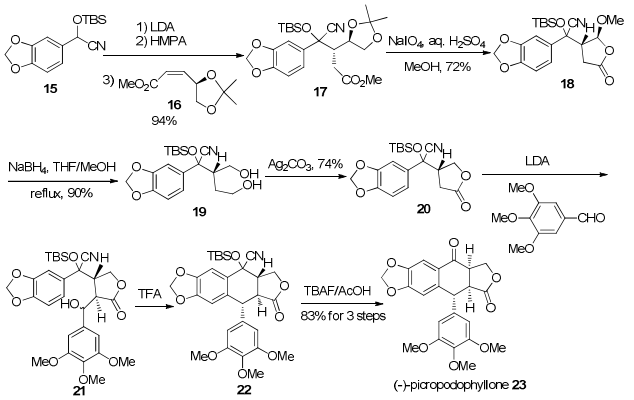
2.2 Chiral pool strategy

The chiral pool strategy is broadly adopted in enantioselective synthesis in natural product, and this approach was applied in the first try to get aryltetralin optically by Koga (Scheme 3).[13] The synthesis commenced with chiral γ-lactone **8** which was easily accessed from L-glutamic acid.[14] Deprotonation of **8** with LDA (lithium diisopropylamide) at low temperature and the generated enlate reacted with piperonyl bromide to yield **9** as a diastereomeric mixture (79 : 21), favoring the desired trans-3,5-diastereomer due to the presence of bulky Tr protecting group on the α-face of lactone **8**. LAH (lithium aluminium hydride) reduction was followed by hydrogenolysis of the Tr protecting group to afford triol **10**. Thus obtained **10** was still a diastereomeric mixture, but the diastereomerically pure **10** could be obtained by one cycle of recrytallization (60%, 3 steps). The obtained optically pure **10** was then subjected $NaIO_4$ cleavage, and hemiacetal **11** was obtained in an as high as 98% yield. Further oxidation stage adjustment of hemiacetal to lactone was realized via oxidation of **11** with Collins reagent to afford R-**12** (98%). Aldol condensation of the enolate form of **12** generated by LDA at low temperature with trimethxybenzaldehyde proceeded fluently to furnish **13** as a pair of epimers at the freshly generated alcohol site (83%). Finally, cyclization of the B ring was effected with TFA with high yield and diatereoselectivity to generate (-)-isodeoxypodophyllotoxin **14** (96%).



Scheme 3. Enantioselective synthesis of (-)-isodeoxypodophyllotoxin (**14**) with **8** as chiral starting material.

During the asymmetric synthesis of (-)-picropodophyllone, Ohmizu et al. also adopted the chiral pool strategy, and chiral *Z*-α,β-unsaturated ester **16** derived from chiral glyceric aldehyde was chosen as the starting material (Scheme 4).[15] Thus, The Michael addition between anion generated from **15** with LDA and *Z*-α,β-unsaturated ester **16** proceeded with high yield and de selectivity at the presence of HMPA (94% yield, 93% de). The high stereoselectivity was determined by both the high coordination ability of HMPA to lithium species and the 1,3-allylic strain.[16] The Michael adduct **17** was then treated with sodium metaperiodate in methanol to give the γ-lactone **18** in 72% yield. Reduction of **18** under the effect of sodium borohydride in hot THF-methanol followed by selective oxidation of the resulting diol **19** with Fetizon reagent (Ag_2CO_3 on Celite) afforded the γ-lactone **20** in 67% yield (2 steps). The following Aldol condensation between **20** and 3,4,5-trimethoxybenzaldehyde was carried out in THF at -78 °C using LDA as promoter to generate **21**, which was further converted to cyclized compound **22** under the effect of TFA in dichloromethane at room temperature. Subsequently, **22** without purification was treated with TBAF/HOAc to release the carbonyl group at the C-4 and simultaneously epimerize the 3-carbon chirality to finish the total synthesis of (-)-picropodophyllone **23** (83%, for 3 steps).



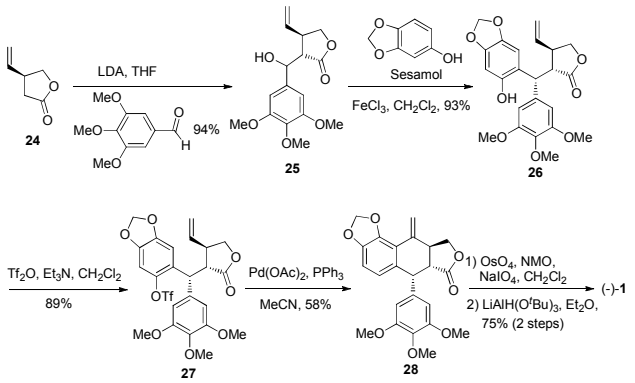
Scheme 4. Enantioselective synthesis of (-)-picropodophyllone **23** with **16** chiral starting material.

Also based on this strategy, Choy reported the synthesis of (-)-epiisopodophyllotoxin by anionic Diels-Alder addition between lithio-α-oxy-α'-aryl-o-quinodimethane and chiral butenolide.[17]

Chiral pool strategy is widely used in natural product synthesis, and its potential has been fully demonstrated by the synthesis of numerous complex natural products. In the above discussed synthetic cases capitalizing on chiral pool strategy, the chiral centers contained in the chiral pool starting material was not maintained in the final products, instead was removed during the synthesis. In consequence, the whole synthetic efficiency is compromised, and big improving room is left.

To overcome the inherent shortcomings of chiral pool strategy as mentioned above, Bach et al. devised an elegant route to generate podophyllotoxin **1** entiomerically (Sheme 5).[18] Taniguchi lactone **24**, which is accessible in enantiomerically pure form, condensed with 3,4,5-trimethoxybenzaldehyde with excellent eantioselectivity regarding the stereogenic center α to the lactone, generating **25** in a high 94% yield. The low enantioselectivity with respect the incipient benzylic alcohol was of no relevance, as the projected subsequent Friedel-Craft alkylation proceeded via S_N1 substitution mechanism. Thus, under the catalysis of $FeCl_3$, **25** reacted with sesamol enantioselectively to give **26** in excellent chemical yield (93%). To cyclize the B ring, an intramolecular Heck reaction was applied. To this end, the free phenolic OH in **26** was transformed to its triflate under

standard conditions to give **27** (89%), which is ready for intramolecular Heck reaction. Upon treated with $Pd(OAc)_2$ at the presence of PPh_3 as ligand, a pretty good yield of alkene **28** was isolated (58%). Oxidative cleavage of the terminal alkene was followed by stereoselective reduction of the resulting carbonyl group at C-4 led to (-)-podophyllotoxin **1** (75%, 2 steps). Because appropriate chiral pool was selected as well as no protecting group manipulation was involved, the total synthetic steps were reduced to 6, and thus the whole synthetic efficiency was improved dramatically (35% overall yield).



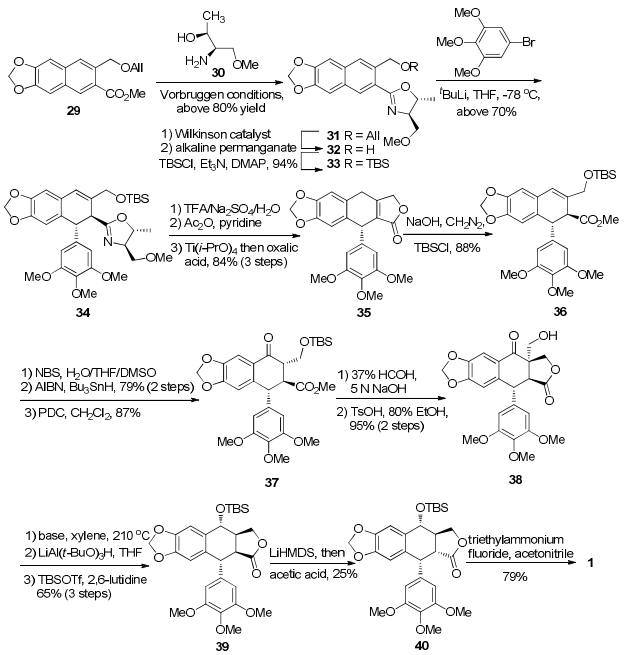
Scheme 5. Total synthesis of (-)-podophyllotoxin **1** via chiral pool **24**

2.3 Chiral auxiliary strategy

Chiral auxiliary strategy is the most frequently applied strategy in enantioselective aryltetralin synthesis. The strategy was first introduced to this field by Meyers, and was then widely accepted by other groups.[19-41] A variety of chiral auxiliaries including chiral oxazoline, chiral oxazolidine, (-)-menthol, methyl mandelate, chiral sulfoxide, and chiral guanidinimu salt have been used.

2.3.1 Chiral oxazoline auxiliary

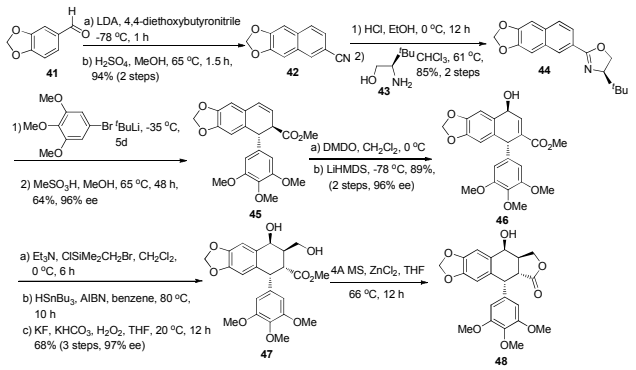
Leveraging on chiral oxazoline auxiliary, in 1988 Meyers and co-workers finished the first total synthesis of (-)-podophyllotoxin (Scheme 6).[19] The synthesis started with naphthoic ester **29**, which was treated with methoxyamino alcohol (+)-**30** in the presence of $Ph_3P/CCl_4/Et_3N$ (Vonbruggen conditions), [20] producing **31** with the appropriate auxiliary in place in above 80% yield. Removal of the All protecting group was realized by isomerization to vinyl ether under the effect of Wilkinson catalyst, and subsequent cleavage with permanganate afforded **32** in 68% yield (2 steps). The free OH group in **32** was reprotected with TBS group under standard conditions to generate silyl ether **33** (94%). After finishing the protecting group manipulations, now the stage was set for the key asymmetrical arylation. Thus, the trimethoxyaryllithium generated by bromide-lithium exchange under the effect of ^{t}BuLi reacted with **33** without any incident at -78 ^{o}C, affording, after quenching with ^{i}PrOH, **34** in high chemical yield and high stereoselectivity (70-80% yield, dr = 98 :2). The removal of the chiral oxazoline auxiliary in **34** was proved to be not a trivial problem, and three steps were required. Under the effect of TFA/Na_2SO_4, the oxazoline moiety was converted to unstable ester ammonium salt, which was then acetylated to afford the stable acetate-acetamide intermediate. Transesterification promoted by $Ti(OiPr)_4$[21] was followed by cyclization catalyzed by aqueous oxalic acid, converting the acetate-acetamide intermediate to (+)-β-apopicropodophyllin **35** (84%, 3 steps). The transesterification conditions could also bring about the double bond migration from C-3,4 to C-2,3. Saponification of the lactone moiety in **35** and the resulting carboxylic acid and OH was successively protected as methyl ester and TBS ether to generate **36** (88%). During the saponification process, the double bond in **36** was retrieved to the original C-3,4 position. To introduction of 4-OH, a two-step reaction sequence was adopted, that is bromohydrination with NBS and subsequent radical debromination (79%, 2 steps). In the obtained intermediate, the stereochemistry at C-3 was epimeric with C-3 in the target molecule (-)-podophyllotoxin. Epimerization at C-3 was the optimal choice for the authors. To this end, oxidation of 4-OH to carbonyl group was required to facilitate the programmed epimerization. Thus, oxidation of alcohol intermediate with PDC produced **37** in a good 87% yield. Unfortunately, the tries to inversion the chirality at C-3 only met with failure. In consequence, a detour tactic was applied to realize the desired conversion, in which formaldehyde aldol reaction, acidic lactonation were involved (95%, 2 steps). The resulting lactone **38** was then subjected to retro-aldol reaction to extrusion of formaldehyde, yielding *cis*-fused 6/5-lactone. $LiAl(^tBuO)_3H$ reduction followed by silylation with TBSOTf furnish **39** (65%, 3 steps), which only has its C-2 chirality epimeric to natural podophyllotoxin. Finally, deprotonation of C-2 with LiHMDS (lithium bis(trimethylsilyl)amide) and quenched with acidic acid at -78 ^{o}C yielded an equilibrium between the desired compound **40** and starting material **39**, favoring the starting material **39** more (39 : 40 = 1.7 : 1, 25% yield). Desilylation of **40** with Et_3NHF afforded (-)-podophyllotoxin **1** (79%).



Scheme 6. The first total synthesis of (-)-podophyllotoxin **1** with oxazoline auxiliary stategy.

The first total synthesis of **1** achieved by Myers and co-worker has a profound effect on enantioselective synthesis of aryltetralin derivatives, although the whole synthetic efficiency was seriously compromised by the long synthetic steps resulting from two inefficient chirality inversions at both C-2 and C-3.

Inspired by Myers' seminal work, Linker et al. reported a much more concise and highly efficient approach to generate aryltetralin derivative (-)-epipodophyllotoxin relying on oxazoline auxiliary (Scheme 7).[22] Commercially available piperonal **41** was used as starting material, and it was converted nitrile **42** efficiently via aldol reaction with 4,4-diethoxybutyronitrile under the effect of LDA at low temperature and cyclization-dehydration process catalyzed with acid (94%, 2 steps). Upon treated with HCl and EtOH, the nitrile functional group was transformed to ethyl ester, which was then condensed with chiral amino alcohol **43** to afford oxazoline **44** with the desired chiral auxiliary installed in place (85%, 2 steps). In the subsequent asymmetric Michael addition step, similar procedure as that used in podophyllotoxin synthesis by Myers was adopted, that is, the trimethyoxyphenyllithium species generated by bromide-lithium exchange attack **44** α-selectively at -78 °C. Nevertheless, in this case, the following quenching step and auxiliary removal step was combined into one step, wherein methanesulfonic acid was used to protonation of the aza-enlate and conversion the chiral auxiliary to methyl ester as well to furnish **45** in high yield (64%, 2 steps, 96% ee). Influenced by the α-oriented phenyl group, epoxidation of **45** with DMDO (dimethyl dioxirane) preferentially afforded β-epoxide, which was then treated with LiHMDS to effect epoxide opening to generate allylic alcohol **46** (89%, 2 steps, 96% ee). Intermediate **46** was ready for the subsequent silicon-tethered intramolecular radical cyclization.[23] Thus, the radical precursor was installed by silylation of the allylic alcohol in **46** with commercially available bromomethylchlorosilane. Upon treated with $HSnBu_3$, bromomethylsilane underwent radical cyclization reaction to present siliconcycle-containing intermediate. The silicon tether contained in cyclized intermediate was then conveniently removed by Tamao oxidation,[24] thus diol **47** was obtained (68%, 3 steps, 97% ee). The freshly constructed C-3 chiral center was formed with exclusive regio- and stereoselectivity thanks to the existing β-oriented 4-OH. At this junction, what remained to finish the total synthesis was to complete the formation of the lactone. This was realized under the catalysis of $ZnCl_2$ to get (-)-epipodophyllotoxin **48** in high yield (98%).

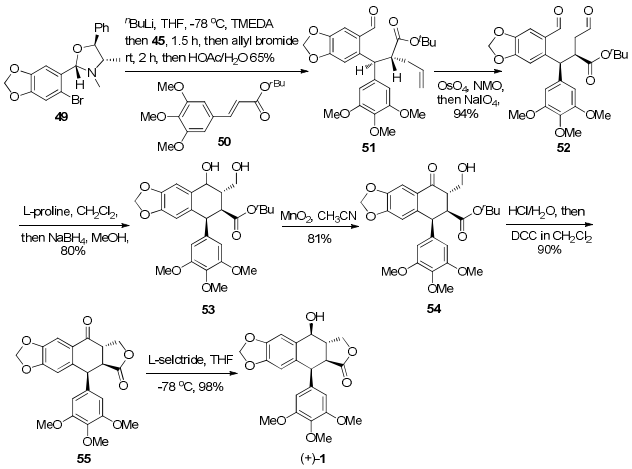


Scheme 7. Enantioselective synthesis of (-)-epipodophyllotoxin **48** with simplified oxazoline auxiliary.

2.3.2 Chiral oxazolidine auxiliary

Also applying the chiral auxiliary strategy, Zhang's endeavor to synthesize (+)-podophyllotoxin is quite novel, not only because oxazolidine auxiliary was used but also because a sequential asymmetric Micheal addition-allylation protocol was adopted to forge the required C-1 and C-2 chiral centers (Scheme 8).[25] Phenyl bromide **49** carrying the oxazolidine auxiliary was produced form bromopiperonal and commercially available pseudoephedrine (95%). The pivotal conjugate addition-allylation-auxiliary removal sequence was effected with ^{n}BuLi and HOAc, respectively, with nBuLi promoting the conjugate addition as well as allylation at the presence of TMEDA while HOAc catalyzing auxiliary removal, generating **51** with good yield and excellent diastereo- as well as enantioselectivity (65% yield, dr = 96.8%, ee = 98.6%). The high diastereo- and enantioselectivity derived from the high coordination propensity of the *N* atom on the chiral auxiliary ring to lithium on the aryl ring, rendering the oxazolidine ring and the aryl ring in the same plane; while the bulky phenyl substitute on the oxazolidine ring dictate from which face **50** approached the aryl lithium. After the Michael addition taking place, the resulting enolate lithium could also complex with *N* atom of the oxazolidine ring, further determining the attacking direction of the allyl group. Thus, in this case, the auxiliary influenced the chiral center builts of both C-1 and C-2 at the

same time. With the key intermediate **51** in hand, the superfluous one carbon was removed via dihydroxylation and oxidative cleavage sequence to afford dialdehyde **52** (94%, 2 steps). Under the catalysis of L-proline in CH_2Cl_2, **52** underwent aldol condensation to generate β-OH aldehyde enantioselectively which was reduced directly with $NaBH_4$ at the same pot, producing **53** as a mixture of epimers at C-4 (80%). MnO_2 mediated regioselective benzylic OH oxidation afforded ketone ester **54** (81%). Removal of the carboxylic protecting group was followed by intramolecular esterification, producing lactone **55** (90%). Finally, stereoselective reduction of 4-carbonyl group was achieved by L-selectride at -78 °C to get the target molecule (+)-**1** in 98% yield.

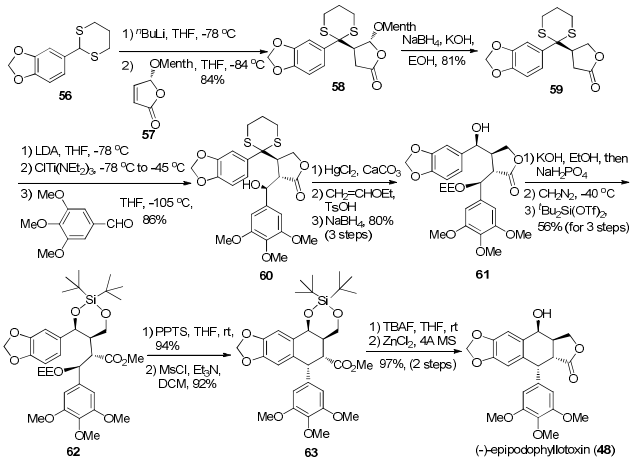


Scheme 8. Total synthesis of (+)-podophyllotoxin **1** with oxazolidine auxiliary.

2.3.3 Menthol auxiliary

(-)-Menthol is an important chiral auxiliary used in enantioselective synthesis of aryltetralin. Its auxiliary effect is exerted by in combination with butenolide to form chiral Feringa synthon,[26] and through the efforts of Pelter and co-workers enantiomerically pure Feringa synthon is now cheaply and readily available.[27] Capitalizing on menthol auxiliary, two protocols to reach enantioselective synthesis of aryltetralins have been devised, that is, the successive Micheal addition-aldol condensation protocol and D-A cyclization protocol.

The menthol auxiliary strategy was first introduced to asymmetric synthesis of aryltetralin derivatives by Vandewalle et al., leading to the enantioselective total synthesis of (-)-epipodophyllotoxin **48** (Scheme 9).[28] Conjugate addition of lithium anion of **56** to the chiral butenolide **57** proceeded stereoselectively and efficiently to produce the desired 1,4-adduct **58** (84%). Thus, the chirality was successfully transmitted from the menthol auxiliary to C-3 stereocenter of aryltetralin. Removal of the auxiliary group and reduction of the resulting aldehyde functional group was realized via base-catalyzed hydrolysis and $NaBH_4$ reduction to afford lactone **59** without racemization (81%). Treatment of **59** with LDA at -78 °C, followed by transmetallation with tris(diethylamino)-titaniumchloride[29] and subsequent addition of trimethoxybenzaldehyde at -105 °C, afforded the desired isomer **60** (86%). $HgCl_2/CaCO_3$ mediated hydrolysis of the thioketal, protection of 1-OH with EE and reduction of the resulting 4-carbonyl group converted **60** to intermediate **61** (80%, 3 steps). The conversion of **61** to **62**, wherein lactone hydrolysis, free acid methylation, and silylenation of 1,3-di-OH were involved, was proved to be quite difficult, and special cautions should be taken. Thus, basic hydrolysis of the lactone moiety in **61** was effected with ethanolic potassium hydroxide, the obtained potassium carboxylate was then neutralized with phosphate buffer at -5 °C. Thus obtained free carboxylic acid functionality was immediately methylated with ethereal diazomethane at -40 °C under the condition of exclusion even trace amount of acid, producing dihydroxy-methyl ester which was immediately subjected to silylenation contions (di-*tert*-butylsilylditriflate, 2,6-lutidine) at low temperature to generate **62** (56%, 3 steps). It should be noted that in order to get reasonable overall yield of the three sequential steps, the reactions must be conducted without interruption and at low temperature, otherwise, serious side reactions including relactonization and β-elimination would have taken place. Selective removal of EE protecting group of **62** was conducted under mild acidic condition (PPTS), generating C1-OH which is ready for B-ring cyclization. Mesylation of C1-OH with MsCl at the presence of Et_3N led to exclusive formation of the desired 1,2-*cis*-2,3-*trans* tetralin **63** without detection of the mesylate intermediate (86.5%, 2 steps). Further elaboration of **63** to (-)-epipodophyllotoxin **48** was carried out via desilylation and Lewis acid catalyzed lactonization, affording the target molecule in a high 97% yield (2 steps).

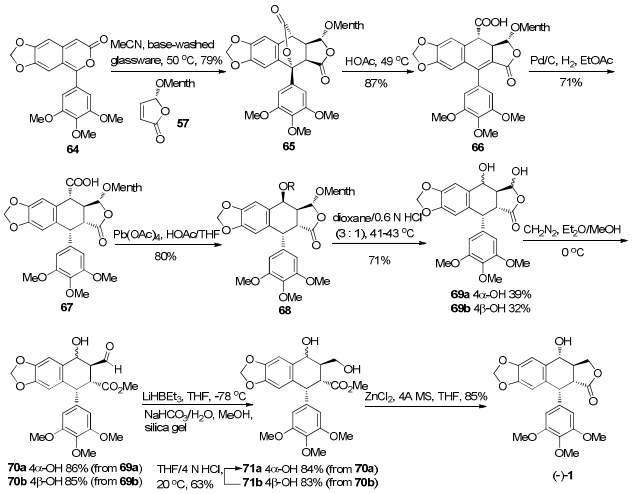


Scheme 9. Total synthesis of (-)-epipodophyllotoxin **48** via menthol auxiliary strategy

Applying the same protocol as used by Vandewalle in the synthesis **48**, Pelter and co-worker finished the asymmetric synthesis of a series of aryltetralin analogues with the all chiral centers induced from chiral synthon **57**.[30]

Also relying on chiral synthon **57** but through the Diels-Alder addition protocol, Jones et al. achieved the total synthesis of (-)-podophyllotoxin **1** in 1993 (Scheme 10).[31] Diels-Alder addition of *o*-quinonoid pyrone **64**, prepared efficiently from

corresponding *o*-carbonyl-substituted phenyl acetic acid under the promotion of Ac_2O, to the chiral dienophile **57** in MeCN in base-washed glassware gave **65** with high facial selectivity and excellent regioselectivity (79%). Eliminative opening of the lactone functional group was promoted by HOAc, affording **66** which was ready for chrality inversion at both C-1 and C-2 simultaneously (87%). The hydrogenolysis of the tetrasubstitued double bond in **66** was proved to be sluggish, but with excellent diastereoselectivity, to produce **67** in 71% yield. The satisfactory facial discrimination was mainly due to the influence exerted by menthol auxiliary, because when the same hydrogenolysis conditions was subjected to similar substrate lacking the auxiliary, α-diostereoselectivity was preferred. The acid **67** with the correct stereochemistry at C-1, C-2 and C-3 was cleanly converted by $Pd(OAc)_4$ oxidation to acetate **68** with chirality at C-4 inverted (80%). Additional prudence was required to hydrolysis of the menthyl auxiliary under controlled acidic conditions to give the lactol **69** as a four-diatereoimer mixture at the lactol carbon and C-4 (71%). **69** could be separated into two groups **69a** and **69b** by silica gel chromatography, and each group was comprised by a pair of epimers at the lactol carbon. **69a** and **69b** were then taken advance separately. Thus, mthylation of **69** with diazomethane produced **70a** and **70b** in 86% and 85% yield, respectively. Reduction of the aldehyde group in **70** was effected with super hydride at low temperature, leading to methyl podophyllate **71a** and methyl epipodophyllate **71b** (84% and 83% yields, respectively). To enhance the whole synthesis efficiency, **71b** was converted to **71a** under the catalysis of 4 *N* HCl. The combined **71a** was then subjected to standard lactonisation conditions ($ZnCl_2$, 4A MS) to furnish (-)-podophyllotoxin **1** (85%).

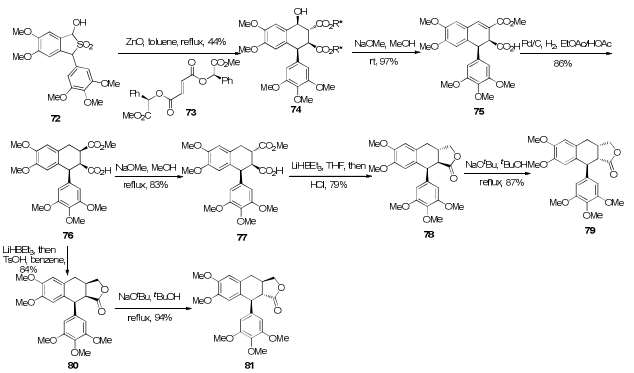


Scheme 10. Total synthesis of (-)-podophyllotoxin **1** via menthol auxiliary strategy

Beside isolable pyrone 64, reactive arylisobenzofuran, generated in situ from hydroxyacetal with acid, can also react with chiral synthon **57** via D-A cycloaddition to build the framework of arytetralin. Taking full advantage of this transformation, Pelter and coworkers realized the asymmetric synthesis of isopodophyllotoxin.[32]

2.3.4 Methyl lactate and methyl mandelate auxiliary

In 1990, Charlton et al. reported a synthetic route to produce podophyllotoxin analog enantioselectively based on Diels-Alder addition wherein *E*,*E*-α-hydroxy-α'-aryl-*o*-quinodimethane and *S*-methyl lactate fumarate were used as diene and dienophile, respectively.[33] Further investigation resulted in the evolvement of the auxiliary from chiral methyl lactate to chiral methyl mandelate.[34] Compared with methyl lactate, methyl mandelate holds 2-fold evident advantages. Firstly, methyl mandelate auxiliary is readily available in both enantiomeric forms. Secondly, it can be easily removed by hydrogenolysis which can avoid undesired epimerization of chiral centers α to the ester group. Capitalizing on this chiral auxiliary, Charlton and co-workers accomplished the synthesis of (-)-dimethylretrodendrin and its diastereomers (Scheme 11).[35] Thus, as the precursor of *E*,*E*-α-hydroxy-α'-aryl-o-quinodimethane, sulfone **72** and methyl (*R*)-mandelate fumarate **73** reacted fluently in toluene in the presence of ZnO, generating **74** in a moderate 44% yield. Treatment of the cycloadduct **74** with NaOMe at rt gave the elimination product **75** in 97% yield, successfully realizing the discrimination of C-3 and C-4 esters. In this conversion a tandem lactonization/base-induced elimination process was involved. Catalytic hydrogenation of **75** provided the all-*cis* compound **76** (86%), as the pivotal intermediate to produce the target molecules. Regioselective epimerization of C-3 ester was achieved under basic conditions, generating **77** in 83% yield. The chiral integrity at C-2 was kept intact due to the formation of sodium carboxylate of the free carboxylic acid group in **76** under basic conditions reduced the acidity of the protons residing on C-2. Super hydride reduction of the ester group was followed by lactonization under the catalysis of acid to generate (+)-isodimethylretrodendrin **78** (79%). The resulting lactone in **78** was further treated with strong base could lead to the epimerization on C-2 to furnish (-)-isopicrodimethylretrodendrin **79** (87%). When **76** was subjected to the reduction and lactonization conditions directly, then (+)-picrodimethylretrodendrin **80** was obtained efficiently (84%). Finally, inversion the C-2 stereocenter was successfully conducted with ^{t}BuONa, producing (-)-dimethylretrodendrin **81** in 94% yield.



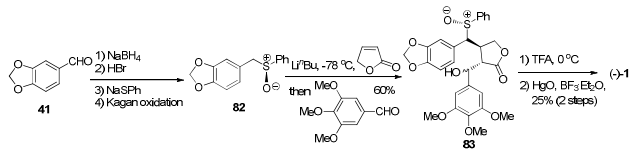
Scheme 11. Enantioselective synthesis of aryltetralin derivatives induced by methyl mandelate auxiliary

Switching the auxiliary from methyl (*R*)-mandelate to its *S*-entiomer, the asymmetric synthesis of (-)-neopodophyllotoxin was also accomplished by Charlton et al in 1992.[36] Changing the precursor of *o*-quinodimethane from cyclic sulfone to benzocyclobutenol could facilitate the synthesis of 4-deoxy-arytetralin. Thus, an asymmetric synthesis of (-)-deoxypodophyllotoxin was achieved by the same group applying the same strategy used above.[37]

Because the absolute stereochemistry of the cycloadduct is controlled by the absolute stereochemistry of the chiral auxiliary and both entiomers of methyl mandelate are easily available, this strategy enjoys high flexibility, as exemplified by the highly efficient synthesis of neopodophyllotoxin and dimethylretrodendrin diastereomers.

2.3.5 Chiral sulfoxide auxiliary

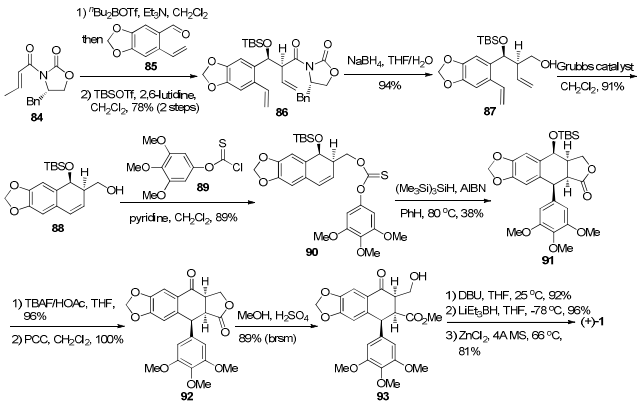
As useful chiral auxiliaries in asymmetric synthesis,[38] chiral sulfoxides also find application in the enatioselective synthesis of aryltetralin (Scheme 12).[39] Piperonal **41** was transformed to chiral sulfoxide **82** via four conventional steps including carbonyl group reduction, bromide introduction, thiophenolate substitution, and Kagan asymmetric oxidation of sulfide to sulfoxide. The resulting **82** was then put to tandem Micheal addition/aldol condensation reaction sequence with but-2-en-4-olide and 3,4,5-trimethoxybenzaldehyde under the catalysis of Li^{n}Bu at -78 ^{o}C, affording **83** in a good 60% yield in one-pot. Acid mediated cyclization and auxiliary removal with HgO and $BF_3{\cdot}Et_2O$ generated (-)-podopyllotoxin **1** (25%, 2 steps). This represent one of the most concise enantioselective synthetic route to generate podophyllotoxin, however, further refinement is required to improve the whole synthetic efficiency.



Scheme 12. Asymmetric synthesis of (-)-**1** with chiral sulfoxide as auxiliary

2.3.6 Evans auxiliary

The powerful Evance oxazolidinone also has impressive performance in aryltetralin synthesis, as exemplified by Sherburn's ingenious synthesis of (+)-podophyllotoxin, featuring with the highly efficient raical-induced intramolecular carboxyarylation (Scheme 13).[40] The synthesis began with Evans *syn*-aldol reaction between the dibutylboronenolate of crotonyl oxazolidinone **84** and 6-vinyl piperonal **85**, and, after protection of the incipient OH with TBS, intermediate **86** was obtained in a good 76% yield. Reductive removal of the oxazolidinone in **86** was effected with $NaBH_4$ to afford **87** (94%), which was then subjected to RCM reaction with the first generation Grubbs catalyst to afford **88** in high yield (91%). Thionocarbonation of the primary OH in **88** with chlorothionoformate **89** produced **90** (89%), ready for the pivotal intromolecular carboxyarylation. Thus, promoted by tris(trimethylsilyl)silane, the challenging process indeed took place, and 38% yield of the desired **91** was isolated. Desilylation with buffered TBAF and oxidation of the resulting 4-OH with PCC gave (+)-isopicropodophyllone **92** (96%, 2 steps), which was then put to acid-catalyzed tranesterification to give methyl ester **93** (89%, brsm). Compound **93** was then converted to (+)-**1** via a three-step sequence in which selective epimerization at C-3, stereoselective ketone reduction, and tans-lactone formation were involved (71.5%, 3 steps).

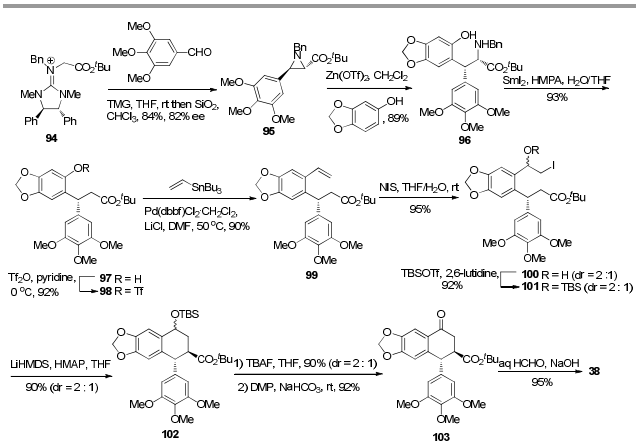


Scheme 13. Asymmetric synthesis of (+)-podophyllotoxin **1** with Evance auxiliary

2.3.7 Chiral guanidinium salt auxiliary

In all above discussed auxiliary protocols, except the step to introduce the auxiliaries, additional steps are required to remove them, hence the overall synthetic efficiency is compromised. Furthermore, in most cases, the applied auxiliaries are destroyed during the detaching steps and can not be reused, which is conflict with the widely accepted atom-economic concept. This situation was improved by Ishikawa et al. who exploited the application of (*R*,*R*)-guanidinium salt **94** in his enantiomerical synthesis of **38** which acted as important intermediate in Meyers total synthesis of (-)-**1**.[41] In comparison to other frequently used auxiliaries, (*R*,*R*)-guanidinium salt **94** has two evident advantages. Firstly, it is a traceless chiral auxiliary, and no additional steps are required to remove it. Secondly, as the departure form, (*R*,*R*)-urea can be easily recovered and recycled to prepare **94**. In the chiral induction step, guanidinium salt reacted with 3,4,5-trimethoxybenzaldehyde to give trans-aziridine **95** in 84% yield and 82% ee. The subsequent ring opening of **95** with sesamol catalyzed by Lewis acid was investigated systematically, and $Zn(OTf)_2$ was demonstrated to be the optimal choice, affording the ring-opened product **96** in high yield (89%) and high diastereoselectivity (dr = 10 : 1). C-N bond cleavage of **96** was effected with SmI_2, accompanied by THF, HMPA, and water serving as solvent, additive, and proton source, respectively, to give ester **97** (85%). The phenolic OH in **97** was transformed to triflate **98** with triflic anhydride (92%), which was followed by Still coupling with tributylvinyltin to give the key intermediate

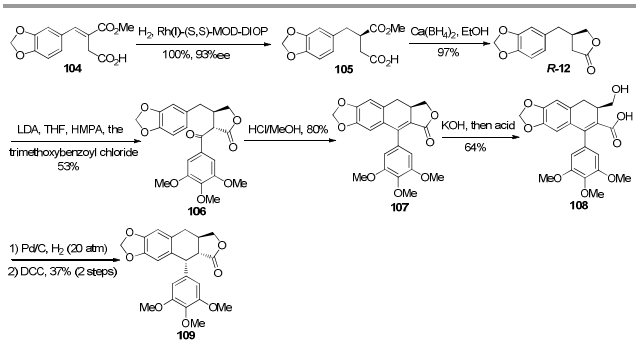
99 (90%). At this junction, the chiral purity of **99** was improved from 81% to 99% via recrystallization from hexane/MeOH. Iodohydrination of **99**, after blocking the incipient OH with TBS, gave **101** via compound **100** (87%, 2 steps). Iodohydrin **101** was then subjected to base-promoted cyclization to yield **102** (90%), followed by TBAF promoted TBS removal and DMP oxidation to afford ketone ester **103** (92%, 2 steps). Aldol condensation of the resultant **103** with excess formalin solution smoothly provided (-)-3-(hydroxymethyl)picropodophyllone **38**, the key intermediate used by Meyers in his total synthesis of (-)-podophyllotoxin. Thus, with **38** in hand, a formal total synthesis of (-)-podophyllotoxin was achieved.



Scheme 14. Enantiomericall sythesis of **38** with chiral guanidimium salt as chiral auxiliary

2.4 Catalytic asymmetric hydrogenation strategy

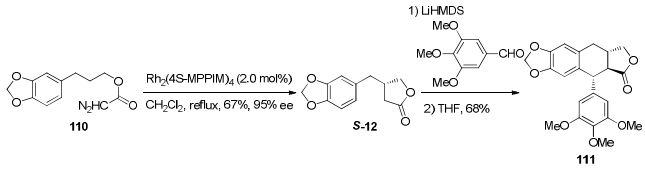
Although in asymmetric synthesis of aryltetralin field the auxiliary strategy has been attracting the major attentions of chemists and big progress has been made, the inherent drawback of this strategy is quite obvious, that is, at least stoichiometric amount of chiral source is required which is generally destroyed in the removal step and can not be recovered. In this regarding, stereogenic synthesis of aryltetralin via chiral catalyst (chiral reagent-controlled strategy) is highly desirable, as in this case only catalytic amount of chiral ligand is necessary. In line with this direction, Achiwa devised an ingenious synthetic route to get arytetralin derivatives enantiometrically, featuring with highly efficient chiral center construction via asymmetric hydrogenation catalyzed by chiral Rh(I) complex (Scheme 15).[42] The asymmetric synthesis of (-)-deoxypodophyllotoxin **109** was commenced with arylidenesuccinic acid mono-methyl ester **104**, derived easily by Stobbe condensation of dimethyl succinate and the corresponding benzaldehyde.[42] The key asymmetric hydrogenation of **104** was catalyzed by Rh(I)-(*S*,*S*)-MOD-DIOP complex in a hydrogen atmosphere, affording acidic ester **105** in quantitative yield and 93% ee. It should be noted that the molar ratio between substrate and rhodium(I) complex could reach as high as 500. Selective reduction of ester functionality in **105** and concomitant lactonization was effected with calcium borohydride to generate *R*-**12** which also acted as intermediate in Koga's synthesis of isodeoxypodophyllotoxin.[13] Lectone **12** was subsequently acylated with 3,4,5-trimethoxybenzoyl chloride to give podorhizon **106** (70%), which was followed by dehydrative ring-closure under acidic condition to produce **107** (80%). Saponification of **107** with NaOH followed by acidification furnished **108** in 64% yield. Intermediate **108** was then converted to **109** through hydrogenation and lactonization (37%, 2 steps). Direct hydrogenation of **107** only gave all cis-isomer of **109**, thus a two-step sequence was adopted to obtain **109**.



Scheme 15. Asymmetric synthesis of **109** via asymmetric hydrogenation

2.5 Catalytic asymmetric C-H carbine insertion

Another example based on chiral reagent-controlled strategy came from Doyle's work, in which the chirality was introduced through catalytic asymmetric C-H carbine insertion (Scheme 16).[43] The key asymmetric carbine C-H insertion of diazoacetate **110** was catalyzed with only 2.0 mol% of chiral Rh(II) catalyst to give lactone *S*-**12** in 67% yield and 95% ee. Conversion of *S*-**12** to **111** entailed aldol condensation of *S*-12 with 3,4,5-trimethoxybenzaldehyde and acid mediated Friedel-Crafts ring closure (68%, 2 steps).



Scheme 16. Synthesis of **111** via asymmetric carbine C-H insersion

2.6 Chemo-enzymatic strategy

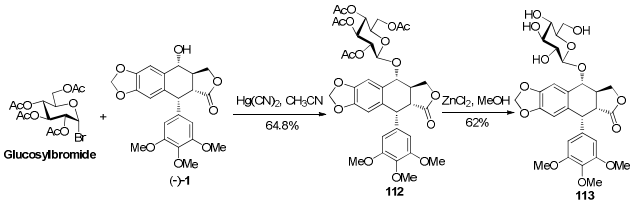
Chemo-enzymatic strategy has found frequent application in bioactive oligosaccharide synthesis,[44] and this strategy was also tried in the field of enantiomerical synthesis of aryltetralin.[45] However, different from the impressive performance in carbohydrate synthesis, so far, its introduction to aryltetralin synthesis did not bring about evident improvement, instead, the synthetic route is still lengthy and the overall efficiency is far from satisfactory.

3 Construction of the Key Glycosidic linkage

Stimulated by the outstanding antitumoral activities of aryltetralin derivatives, the synthesis of aryltetralin glycosides can date back to as early as 1968.[46] Although the investigation starting time is quite early and the aryltetralin glycoside synthetic field has experienced almost half a century's development, all synthetic studies focused on 4-OH glycosylation of podophyllotoxin derivatives. Compared to general benzylic OH, the glycosylation of 4-OH of podophyllotoxin derivatives is quite difficult, as it just resides on the benzylic position of an electron-rich aryl ring, thus tends to depart to generate a stabilized benzylic cation under the effect of Lewis acids widely used to catalyzed glycosylation reaction. In the seminal work of Kuhn and Wartburg, two principal protocols have been established, normal glycosylation and inverted glycosylation protocols.[46,48] In the normal glycosylation protocol, the glycosyl residue equipped with activation group at the anomeric position acts as glycosyl donor to condense with acceptor, the 4-OH of podophyllotoxin derivative; while in the reverted glycosylation protocol, the roles of glycosly donor and accepter were inverted, and glycosyl residue with a OH on the anomeric position serves as acceptor while podophyllotoxin derivative acts as glycosyl donor with its 4-OH activated under Lewis acid conditions.

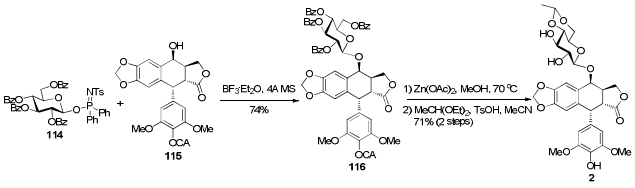
3.1 Normal glycosylation protocol

In the first report regarding normal glycosylation protocol, peracetylated glycosylbromide was selected as glycosyl donor to react with the 4-OH of (-)-podophyllotoxin **1** to afford **112** under the effect of 1.66 equivalents of highly toxic $Hg(CN)_2$ (64.8%, Scheme 17). The resulting **112** was then subjected to deacetylation manipulation to produce podophyllotoxin-β-glucoside. This conversion was proved to be not trivial, because the generally applied Zemplen deacylation conditions could lead to the epimerization of the C-2 chirality of podophyllotoxin. Finally, **112** was exposed to $ZnCl_2$ in MeOH, the desired **113** was obtained in a good 62% yield with the main byproduct generated form the unwanted epimerization of C-2 accompanied by lactone ring opening.[46]



Scheme 17. Synthesis of podophyllotoxin-β-glucoside **113**

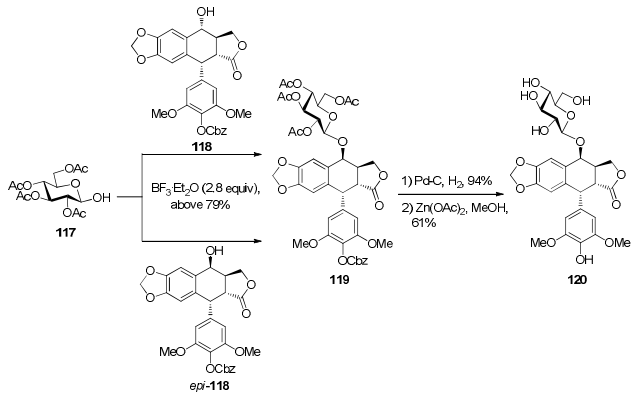
The drawback of the originally established normal glycosylation protocol is that stoichiometric amounts of toxic mercury salt are applied. Nevertheless, the advantage of this method is alluring, as if the acidity of the Lewis acid promoter used in glycosylation step could be controlled appropriately and the activation of 4-OH of the podopyllintoxin accepter was avoided completely, the glycosidic linkage could be constructed stereoselectively both for glycosydic linkage (through anchimeric assistance of 2-*O*-acyl protecting group) and for acceptor C4-OH. To give the best play to the advantage while overcome the shortcoming of this protocol, continuous efforts were made by Ikegami et al. In their modified protocol, a new type of glycosyl donors was applied, and, in turn, the toxic mercury salt was replaced with operator-friendly $BF_3{\bullet}Et_2O$ (Scheme 18).[47] Epipodophyllotoxin **115** was glycosylated with *P*,*P*-diphenyl-N-(p-toluenesulfonyl)phosphinimidate **114** under the promotion of 2.5 equivalents of $BF_3{\bullet}Et_2O$ to afford **116** in a good 74% yield. Treated with mild acidic conditions, all acyl protecting groups were removed without attendant epimerization at C-2, and the resultant intermediate was further acetalized to afford etoposide **2** (71%, 2 steps).



Scheme 18. Synthesis of etoposide **2** with **114** as donor

3.2 Inverted glycosylation protocol

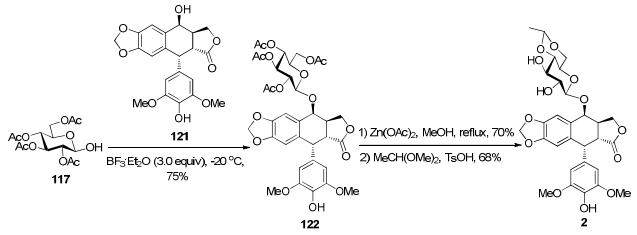
In comparison to normal glycosylation protocol, the reverted glycosylation approach is more frequently applied in arytetralin glycoside synthesis. This protocol was first establishment by Kuhn and Wartburg just behind the normal glycosylation method in the same year (Scheme 19).[48] Under the promotion of $BF_3{\bullet}Et_2O$ (2.8 equiv) at 0-5 ^{o}C, tetra-*O*-acetyl-β-glucopyranose **117** condensed with both podophyllotoxin derivative **118** and epipodophyllotoxin derivative *epi*-**118** to give the same glycoside **119** with above 79% yields. The same glycosylation products demonstrated that the reverted glycosylation proceeded via a S_N1 mechanism, and the chirality of C-4 in podophyllotoxin residue was determined by the α axial-oriented phenyl group which prohibited the attack of the glycosyl anomeric OH from α-face, and thus the epipophollotoxin glycoside was solely obtained. Hydrogenolysis of Cbz protecting group was followed by mild acid mediated deacetylation to convert **119** to **120** (57%, 2 steps).



Scheme 19. Synthesis of podophyllotoxin glucoside **120**

As noted from the work of Kuhn and Wartburg in synthesis of **120** through reverted glycosylation protocol, although the yield of the glycosylation step is higher than that offered by normal glycosylation method, the flexibility of the reverted glycosylation protocol is reduced because it can not be used to generate podophyllotoxin glycoside. In addition, to prepare the pure hemiacetal OH required additional manipulation such as recrystalization, and even the pure form of anomeric OH is applied in the reverted protocol the undesired epimerization may take place during the glycosylation and the α-glycoside can also be formed.

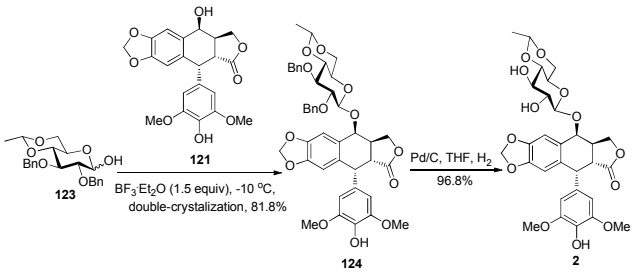
Given that the inverted protocol is superior to the normal one in etopside synthesis, its improvement has never been ceased since its establishment. The synthetic potential of this protocol was further demonstrated by the work from Macdonald's group (Scheme 20).[49] Thus, inverted glycosylation between **117** and **121** afforded glycoside **122** under the promotion of 3.0 equivalents of BF_3•Et_2O (75%). It should be noted that the low concentration (80 mL/mmol) of the substrates in CH_2Cl_2 is a guarantee to get satisfactory glycosylation yield and there was no need to protect the 4'-phenolic OH as well. Deacetylation and acetalization of **122** yield etoposide **2** (47.6%, 2 steps). Counting from **121**, only 3 steps are required to get etoposide, and the overall yield can reach 35.7%.



Scheme 20. Highly efficient synthesis of etoposide **2** through reverted glycosylation protocol

Concerning the difficulty associated with the acquisition of pure β-glycosyl lactol, Allevi et al. found that the TMS form of β-glycosyl lactol could be easily obtained and could be used directly as glycosyl acceptor in the inverted glycosylation protocol. Based on this discovery, alternative route to get etoposide **2** was established.[50]

An even more concise approach was established by Dillon and co-workers, in which only 2 steps counting from **121** are involved and the overall yield could reach as high as 79% (Scheme 21).[51] The synthesis commenced with **123** as a mixture of a pair of anomers. Promoted by BF_3•Et_2O, acceptor **123** condensed with **121** in acetonitrile at -10 °C, after cystalization from acetonitrile at the presence of BF_3•Et_2O and recrystalization from DCM/MeOH after quenching with pyridine, pure **124** was obtained in a high 81.8% yield. The glycosylation process is quite interesting, and deserves further comments. The reaction speed was quite high, and the condensation completed within 10 min, at which time HPLC analysis showed that the glycosylation product existed as a mixture of diastereomers (**124β** : **124α** = 2.4 : 1). After keeping the reaction mixture stand for another 5 h before quenching with pyridine, the ratio between **124β** and **124α** could change to 95 : 5. The ratio enhancement of **124β** mainly resided on the poor solubility of **124β** in the glycosylation media acetonitrile, which made the equilibrium between **124α** and **124β** existed in the reaction mixture shift toward **124β** with the precipitation of **124β** from the reaction solution. Hydrogenolysis of the two benzyl groups in **124** successively afforded etoposide **2** in almost quantitatively yield.



Scheme 21. Concise synthesis of **2** through reverted glycosylation protocol

4 Summary and outlook

To alleviate the environmental and ecological impact imposed by the ever-growing demand of aryltetralin glycosides, a real sense and highly efficient total synthesis approach is highly desirable. Unequivocally, this should represent the development direction of aryltetralin glycoside synthesis field. Although a quite few numbers of synthetic route to generate the aglycon residues have been established based on chiral resolution, chiral pool, chiral auxiliary, catalytic asymmetric hydrogenation, catalytic asymmetric C-H carbine insertion, and chemo-enzymatic synthesis strategies, respectively, at present stage, almost no existing method is suitable to be scalded up and can be competent with the current accessibility manner directly from nature. Even the most concise route to produce podophyllotoxin devised by Bach and co-workers[18] has to be subjected to refinement before accepted as a scalable synthetic route because some toxic and difficult-to-handle reagents are applied. Except for the refinement of the existing

synthetic approaches, emphasis should be laid on the introduction of new methods and synthetic strategies to this field, so as to devise more efficient and competent synthetic routes. The introduction of chemo-enzymatic synthesis strategy to this field by Berkowitz et al. is a brave and helpful try,[45] and all these kind of efforts are welcome and will be beneficial to the development of this field.

For the construction of the key glycosidic linkage, under the frame of the two established normal and reverted glycosylaton protocols, the normal glycosylation protocol is preferred as it can not only control the glycosidic linkage efficiently but also enjoy high flexibility through which both podophyllotoxin glycosides and epipodophyllotoxin glycosides can be obtained, although the reverted glycosylation protocol has impressive performances in etoposide synthesis. To fully demonstrate the potential of the normal glycosylation protocol, new glycosylation methods which can in one hand effect the glycosidic linkage construction efficiently on the other hand keep the acidic labile C-4 OH in podophyllotoxin acceptor intact are highly desirable. In addition to etoposide and teniposide, more and more naturally occurring aryltetralin glycosides are isolated and characterized,[6] and a variety of interesting bioactivities have been demonstrated via preliminary bioactivity investigations. These new developments in aryltetralin glycoside field call on new glycosylation method as well as new protocols, which will undoubtedly have profound effect on the development of new aryltetralin glycoside medicines.

5 Acknowledgements

We acknowledge the financial support from NSFC (21372252 and 21572081) and the Starting Foundation for Doctors of Jiangxi Normal University is highly appreciated.

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Jian-Song Sun received his B. Sc. in chemistry from Qufu Normal University in 2000 and Ph.D. from Dalian Institute of Chemical Physics, Chinese Academy of Sciences, in 2005 (with Prof. B. Yu and X. Han). He then jointed Prof. R. R. Schmidt's group at Konstanz University as a Humboldt postdoctoral fellow. In 2007, he returned to the Shanghai Institute of Organic Chemistry as an associate research professor. In 2014, he then moved to Jiangxi Normal University and was promoted to research professor. His research interests include carbohydrate chemistry and carbohydrate-based therapeutics.

Hui Liu was born in Yichun Jiangxi province. She received her B. Sc. in chemistry from Jiangxi Normal University in 2015 and now she is in pursuit of her master degree in the National Engineering Research Center of Carbohydrate Synthesis in Jiangxi Normal University under the supervision of Prof. J. Sun. Her research focuses on the highly efficient synthesis of bioactive aryltetralin glycosides.

Xiao-Hong Guo graduated from Jianxi Educational Institute in 1985. Then she joined Jianxi Medical College, and in 1992 she moved to Jianxi Normal University. Now, she is the office director of the National Engineering Research Center of Carbohydrate Synthesis in Jianxi Normal University.

Jin-Xi Liao received her B. Sc. from Anhui University in 2006. She completed her Ph.D. at Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (CAS) in collaboration with University of Science and Technology of China (USTC) under the supervision of Prof. B. Yu in 2011. From 2011 to 2014, she worked in Guangzhou Institute of Biomedicine and Health as an assistant research fellow focusing on the development of new medicines. In 2015 she moved to the National Engineering Research Center of Carbohydrate Synthesis in Jianxi Normal University, and now her research interests include total synthesis of naturally occurring bioactive glyconjugates and the developments of new glycosylation methods.