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Research Article

Asymmetric Total Synthesis of Aglacins A, B and E

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Abstract: An asymmetric photoenolization/Diels–Alder (PEDA) reaction, between electron-rich 2-methylbenzaldehydes and unsaturated γ-lactones, was developed to directly construct the basic tricyclic core of aryltetralin lactone lignans. The first asymmetric total synthesis of aglacins A, B and E was achieved based on this newly developed methodology, which enable us to revise the absolute configuration of these natural lignans. This strategy was also used to efficiently prepare naturally occurring aryl–dihydronaphthalene-type lignans (–)-7,8-dihydroisojusticidine B and (+)-linoxepin in four and six steps, as well as 27 members of natural product-like molecules bearing an all-carbon quaternary center at C-8'. We believe that the synthetic aglacins and small-molecule library provide new opportunities to carry out the SAR studies of podophyllotoxin-family natural products.

Introduction

Podophyllotoxin (**1**) was mainly isolated from the rhizomes and roots of Podophyllum species (Figure 1),[1] which belongs to a naturally occurring aryltetralin lactone lignan.[2] This family of natural lignans exhibit a broad spectrum of biological potentials,[3] such as anticancer, insecticidal, antifungal, antiviral anti-inflammatory, neurotoxic, immunosuppressive activities. These properties attracted considerable attentions from both pharmaceutical industry and academic communities, and significant efforts have been made regarding to the chemical synthesis,[4, 5] structure-activity relationships (SARs) and mechanistic studies.[3] Structural modifications of podophyllotoxin have successfully led to several commercially available anticancer drugs as well as drug candidates. For instance, etoposide (**2**, Figure 1) was developed as a topoisomerase II inhibitor, which is clinically used in the treatment of small cell lung cancer and multiform glioblastoma.[6]

Podophyllotoxin (**1**) contains a tetracyclic fused ring including an aryltetralin (A-B ring), two highly oxygenated aromatic rings (A and D rings), a γ-lactone (C ring), and four consecutive chiral centers in B ring (C-7, 8, 7' and 8'). Notabaly, biogenetically related natural products in lower oxidation state were also discovered in nature, such as aglacin A, B, E[7] and linoxepin[8] (**3**, **4**, **5** and **6**, Figure 1). Aglacins were isolated from the methanol extract of the stem bark of *Aglaia cordata* collected in Indonesia by Prokscha and coworkers, which belong to aryltetralin cyclic ether lignans. The structures of aglacins were elucidated by NMR spectral data and X-ray crystallography, and their absolute configuration were determined based on the modified Mosher's method.[7] Interestingly, the relative and absolute stereochemistry of four chiral centers in aglacins were proposed different from those of podophyllotoxin (**1**), which represents the most commonly occurring configuration. Recently, Zhu and coworkers reported an elegant radical-cation cascade under visible-light photoredox catalysis to enable concise synthesis of aryltetralin cyclic ether lignans, including aglacin B, with good yields and excellent diastereoselectivity.[9]

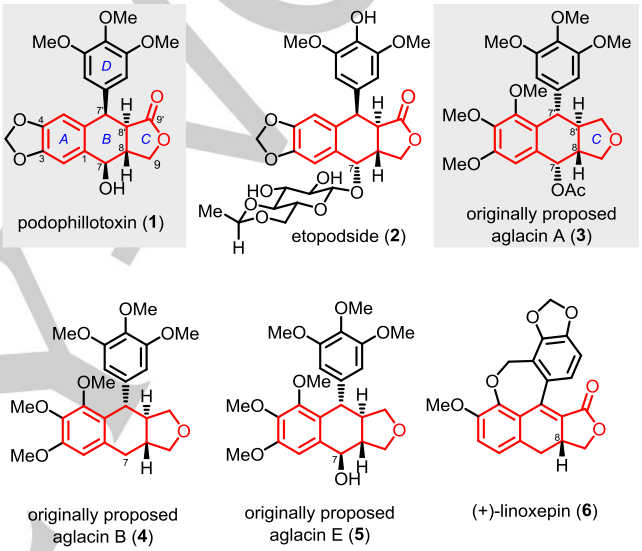

Figure 1. Podophillotoxin, etopodside, originally proposed aglacins and (+)-linoxepin.

Extensive structural modifications and structure–activity relationships of podophyllotoxin have provided comprehensive hints to discover new anticancer lead compounds. However, limited information is available to identify the relationship between the stereochemistry and the biological activities of this family of lignans. We were attracted by the biological potential of natural lignans, and report herein the development of an asymmetric photoenolization/Diels–Alder (PEDA) reaction, between electron-rich 2-methylbenzaldehyde and unsaturated γ-lactone, to directly construct the basic tricyclic core of aryltetralin lactone lignans. Using this strategy, we achieved the first asymmetric total synthesis and absolute configuration revision of aglacins A, B and E. Additionally, a small library of natural product-like lignans (27 examples) were generated for future bioactivity studies.

We envisioned that aglacins A and B might be derived from aglacin E (**5**) by manipulation of the hydroxyl group at C-7 (Scheme 1A). Aryltetralin lactone lignan **7** was designed to serve as a common precursor, which could be converted to aglacin E through a late-stage selective oxidation reaction. In order to construct the core skeleton of lignans, we proposed two pathways based on a key photoenolization/Diels-Alder (PEDA) reaction.[10-11] Pathway A (Scheme 1B): a photo-induced cycloaddition

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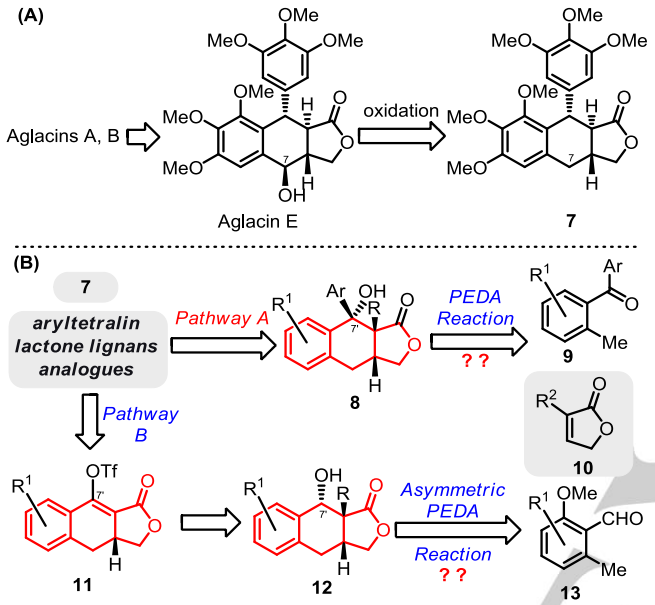
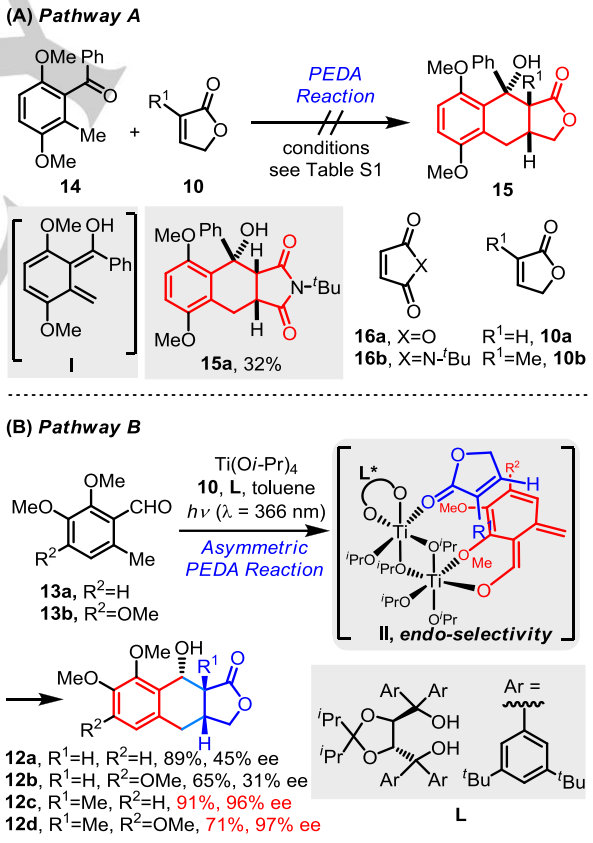
between a benzophenone substrate **9** and unsaturated γ-lactone **10** was devised to directly construct the tetracyclic **8** bearing the basic core of aryltetralin lactone lignans. The challenge of this pathway was how to activate the stereohindered hydroxy-*o*-quinodimethane species, thus undergoing the following Diels-Alder reaction with unsaturated γ-lactone **10**. Pathway B (Scheme 1B): a stepwise approach was planned to form the core skeleton **7** through a metal-catalyzed cross coupling reaction of vinyl triflate **11** and phenylboronic acid. An asymmetric PEDA reaction [12] of electron-rich 2-methylbenzaldehyde **13** and unsaturated γ-lactone **10** was designed to prepare tricyclic compound **12**.



Scheme 1. Synthetic plan.

Results and Discussion

Our research commenced with the key photoenolization/Diels-Alder (PEDA) reaction between fragments **14** and **10** (Pathway A, Scheme 2A). We have disclosed that Lewis acid [Ti(O*i*-Pr)$_4$] plays a key role in the PEDA reaction, which activates inert dienophiles and controls the diastereoselectivity.[12] Accordingly, we extensively investigated the Lewis acid-promoted PEDA cycloaddition of **14** and **10a** (see Table S1 in the Supporting Information), and found that no desired adduct **15** was obtained under the tested conditions. We then explored the photolysis of **14** with the highly reactive dienophiles, including maleic anhydride **16a**, *N*-*tert*-butylmaleimide **16b** and dimethyl fumarate **17**, and only found the formation of **15a** in 32% yield.[13] Principally, photoenolization of **14** would generate a transient hydroxy-*o*-quinodimethane **I** bearing tetra-substituted enol motif (Scheme 2A). It's reasonable to predict the low reactivity of this stereohindered diene species in the following cycloaddition step, even with the highly reactive dienophiles and in presence of the Lewis acid. We then tested the asymmetric PEDA reaction of electron-rich 2-methylbenzaldehyde **13** and unsaturated γ-lactone **10** by a combination of Lewis acid [Ti(O*i*-Pr)$_4$] and a chiral ligand (Pathway B, Scheme 2B). When **10a** was used as a dienophine, the PEDA reactions with **13a** and **13b** gave the desired product **12a** and **12b** in 89% and 65% yield, respectively. However, the enantioselectivities of these reactions were low (up to 45% ee) (see Table S2, S3 in the Supporting Information). In order to improve the stereoselectivity and suppress the background racemic reaction, we envisioned to introduce a methyl group at the α–position of lactone, namely **10b**. We reasoned that this substituted group might help to reduce the rate of cycloaddition and facilitate the formation of chiral Ti-complex. Indeed, we were pleased to observed that the APEDA reaction proceeded smoothly in the presence of catalytic ligand **L** (0.2~0.5 equiv.) and Ti(O*i*-Pr)$_4$ (0.4~1.0 equiv.), and yielded the tricyclic adduct **12c** and **12d** in good yield (up to 91%) and excellent enantioselectivity (up to 97% ee) (see Table S4 and S5 in the Supporting Information). The dosage of Lewis acid highly influenced the efficiency of this reaction, using stoichiomertric amount of Ti(O*i*-Pr)$_4$ gave best reaction yield. A chiral dinuclear species Ti-TADDOLate **II** was proposed to serve as a bifunctional catalyst, which induced an *endo*-cycloaddition in the chiral environment.[12] **12c** and **12d** contain the tricyclic aryltetralin lactone skeleton bearing an all-carbon quaternary center, which differed from the previously reported lead compounds derived from natural lignans.



Scheme 2. Construction of tricyclic core of aryltetralin lactone lignans using asymmetric PEDA reactions.

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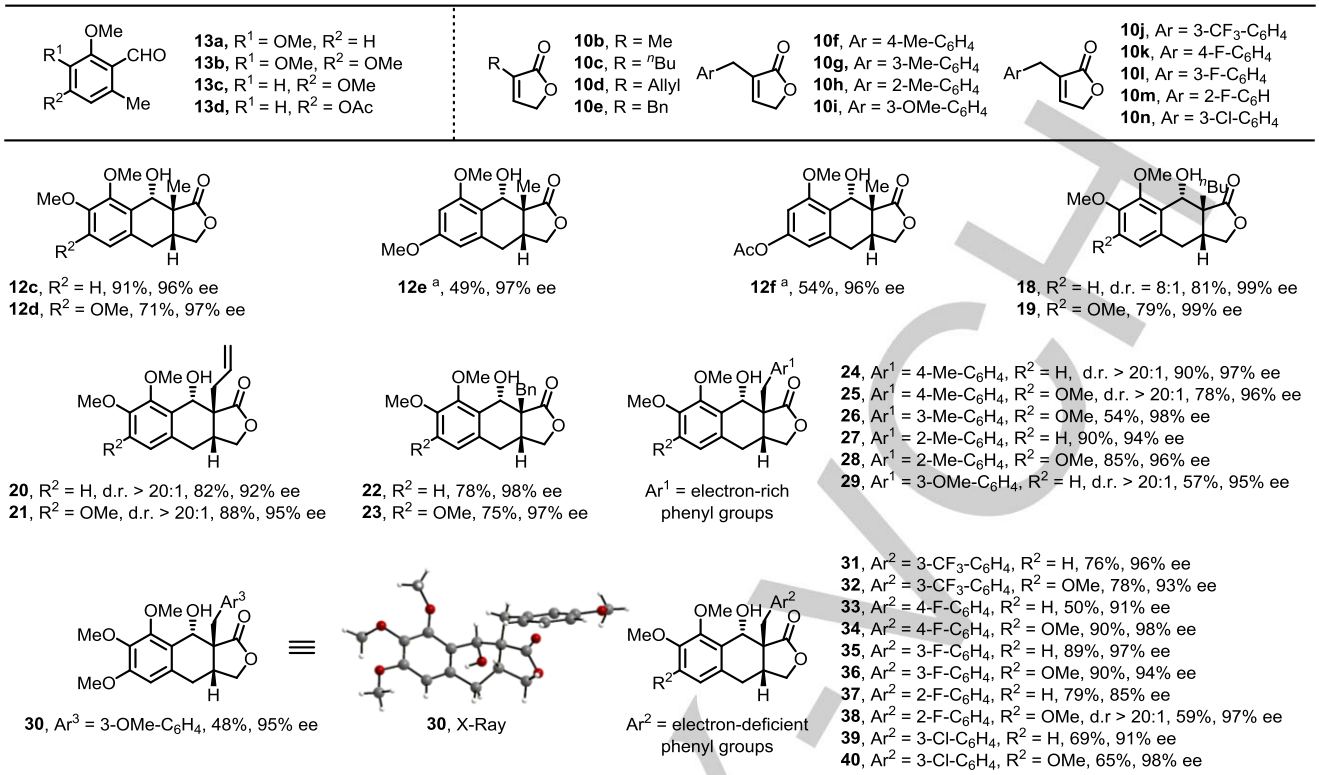

Table 1. Building a small library of aryltetralin lactones. Standard reaction conditions: aromatic aldehyde (0.30 mmol, 1.0 equiv.), dienophile (0.45 mmol, 1.5 equiv.), Ti(O*i*-Pr)$_4$ (0.30 mmol, 1.0 equiv.), **L** (0.15 mmol, 0.5 equiv.), toluene (30 mL, 0.01 M), 30 °C, 50 min. Isolated yields are shown. The ee values were determined by chiral HPLC analys, [a] 0.05 mmol scale.

We were intrigued by the biological potentials of the analogues like **12c** and **12d**, this also promoted us to prepare a small library. As shown in Table 1, using electron rich benzaldehydes (**13a-d**) and α-substituted γ-lactone (**10b-n**) as sterically hindered dienophiles, 27 photo-induced adducts (**12c-f, 18-40**) were efficiently prepared in good yield and enantioselectivities (85%~99% ee) under the standard reaction condition. The products have good diastereoselectivity, wherein the hydroxyl group on the benzylic position has the *cis*-configuration with the electron-withdrawing groups. In order to investigate the roles of substituents on aromatic aldehydes, we carried out the following studies. When the methoxy group at the *ortho* of the aldehyde group was absent or replaced by acetoxy group, we found that no desired adduct was obtained in the PEDA reaction. When the *ortho*-methyl was replaced by benzyl group, the PEDA reaction didn't occur (see Table S6 in the Supporting Information). The aromatic ring contains an electron withdrawing group, such as **13d**, the asymmetric PEDA reaction with lactone **10b** gave **12f** in 54% yield and 96% ee, which was comparable to **12e**. The relative and absolute configuration was determined and confirmed by the X-ray crystallographic analysis of **30**.[14] According to the properties of the substituted groups, these newly formed molecules could be divided into three groups: 1) adducts with acyclic alkyl groups (**12c-f**, **18-23**); 2) molecules bearing electron-rich benzyl groups (**24-30**); and 3) molecules containing electron-deficient benzyl groups (**31-40**).

We then turned our attention to the asymmetric total synthesis of naturally occurring aglacins (Scheme 3). In order to achieve a high enantioselectivity for APEDA reaction, a removable group on the α-position of γ-lactone was necessary. Accordingly, α-bromo lactone **41** was selected as the required dienophile. We then investigated the key APEDA reaction by irradiating a toluene solution of **13b** and **41** in presence of TADDOL-type ligand (**L**, 0.5 equiv.) and Ti(O*i*-Pr)$_4$ (1.0 equiv.) under UV light (λ_{max} = 366 nm), the cycloaddition smoothly occurred and produced the desired tricyclic core **42** as a single diastereomer in 72% yield and 92% ee. Its structure and absolute configuration was confirmed by the X-ray crystallographic analysis.[14] The hydroxyl group on C-7' was then oxidized by 2-Iodoxybenzoic acid and afforded **43** in 82% yield. A regio- and stereoselective oxidation was required to introduce a β-hydroxyl group at C-7. This benzyl C−H oxidation was accomplished through a sequence of radical bromination (NBS/BPO) followed by the hydrolysis of the resulting labile bromide, and produced **44** in 61% yield over 2 steps. After protection of the hydroxyl group as its TIPS ether, we found that bromine could be readily removed by adding sodium thiosulfate during the work-up operation. Then, treatment of the carbonyl group on C-7' with trifluoromethylsulfonic anhydride under basic conditioin furnished the desired triflate **45.** A Pd-catalyzed Suzuki-Miyaura coupling of **45** with aromatic boronic acid **46** led to **47** bearing the required aryl substituent on C-7'. The tetra-substituted C7'=C8' olefin in **47**

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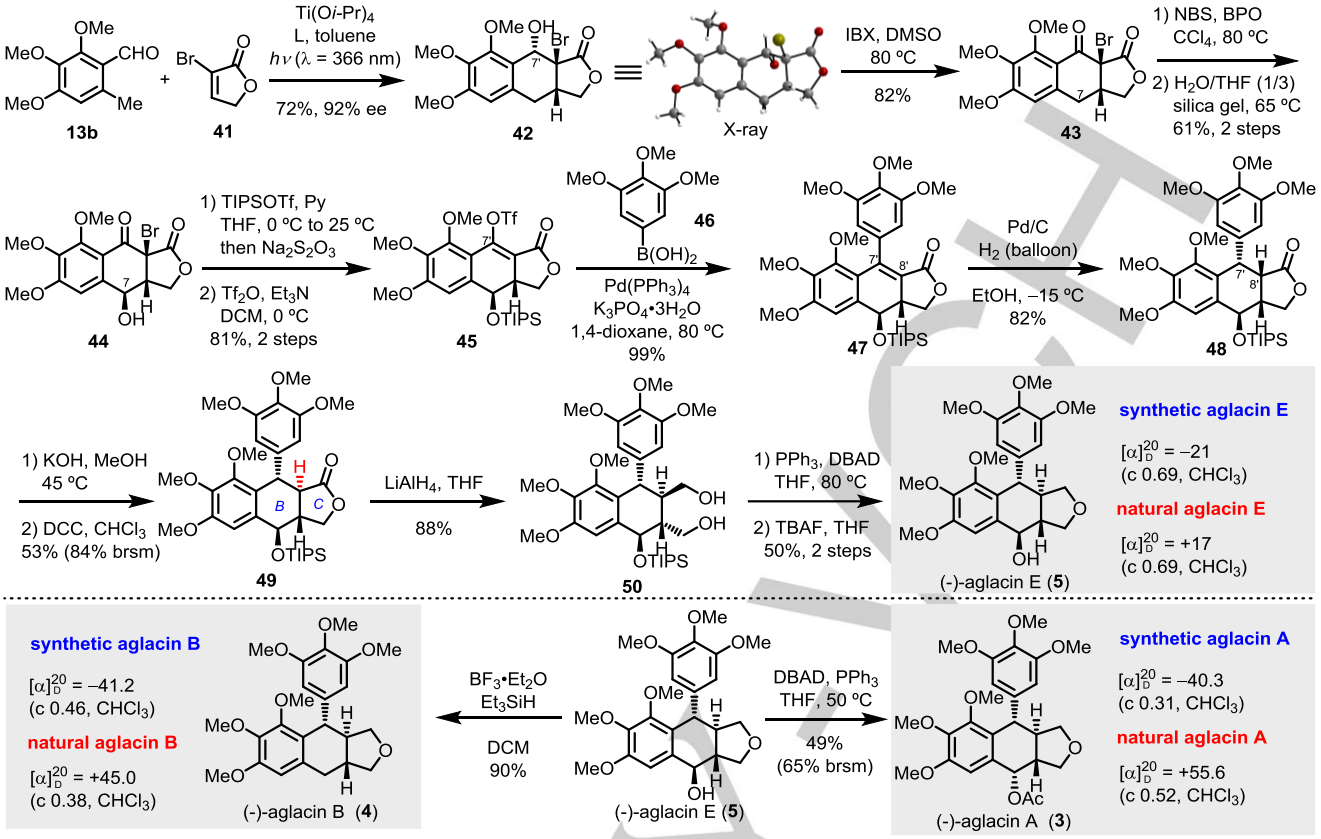
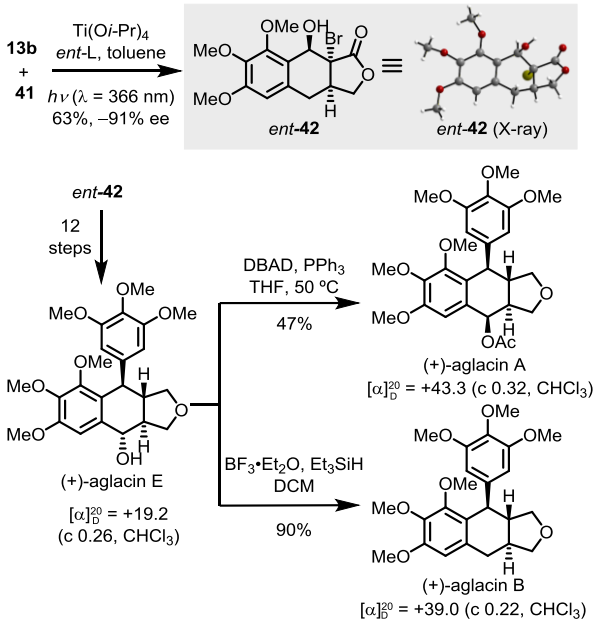


Scheme 3. Total synthesis of (–)-aglacins A, B and E. IBX = 2-iodoxybenzoic acid, DMSO = dimethyl sulfoxide, NBS = *N*-bromosuccinimide, BPO = benzoyl peroxide, Py = pyridine, THF = tetrahydrofuran, TIPSOTf = triisopropylsilyl trifluoromethanesulfonate, Tf_2O = trifluoromethanesulfonic anhydride, DCM = dichloromethane, DCC = dicyclohexylcarbodiimide, DBAD = di-*tert*-butyl azodicarboxylate, TBAF = tetrabutyammonium fluoride.

was selectively hydrogenated at low temperature to give **48** as a single diastereomer in 82% yield. In order to epimerize the C-8' chiral center in **48**, the lactone ring was hydrolyzed under KOH/MeOH, then lactonization was achieved by means of DCC-induced cyclization to construct the *anti*-B-C rings in 84% yield based on the recovery of **48**. Reduction of **49** with lithium aluminum hydride gave diol **50** in 88% yield, and the cyclic ether ring was formed by means of an intramolecular Mitsunobu reaction. A final deprotection of the TIPS group produced aglacin E (**5**) in 50% yield over 2 steps. We found that the NMR data (^{1}H and ^{13}C spectra) of our synthetic aglacin E was in agreement with those of the natural product.[7] However, the newly synthesized **5** ($[\alpha]_D^{20}$ = –21 (c 0.69, $CHCl_3$)) holds an opposite optical rotation to the natural aglacin E ($[\alpha]_D^{20}$ = +17 (c 0.69, $CHCl_3$)). Transformation of (–)-aglacin E to (–)-aglacin A was achieved via an intermolecular Mitsunobu reaction to give (–)-(**3**) ($[\alpha]_D^{20}$ = –40.3 (c 0.31, $CHCl_3$)) in 65% yield based on the recovery of (–)-**5**. Reductive dehydroxylation of (–)-**5** was performed and generated (–)-aglacin B (**4**) ($[\alpha]_D^{20}$ = –41.2 (c 0.46, $CHCl_3$)) in 90% yield.

Indeed, synthetic aglacin A and B from (–)-aglacin E also possess opposite optical rotation to the natural ones, which disclosed (–)-aglacins A, B and E to be the enantiomers of natural aglacins. In order to confirm this proposal, we prepared *ent*-**42**, its absolute configuration was determined by X-ray crystallographic analysis,[14] using *ent*-**L** as a chiral ligand in the APEDA reaction, which was successfully converted to the desired (+)-aglacin A, B and E (Scheme 4). The NMR spectra,



Scheme 4. Total synthesis of (+)-aglacins A, B and E.

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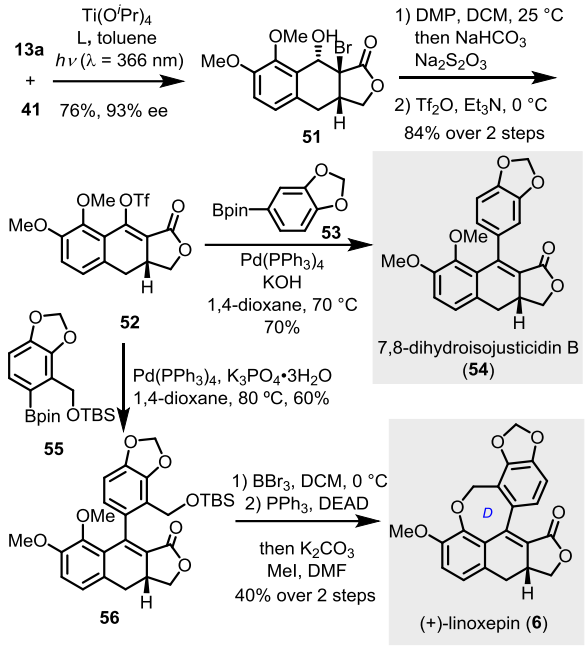

Scheme 5. Total synthesis of (+)-linoxepin and 7,8-dihydroisojusticidine B. DMP = Dess-Martin periodinane, DEAD = diethyl azodicarboxylate.

The high-resolution mass spectrum, and optical rotation of synthetic **3-5** (Table S7 in the Supporting Information) were fully consistent with the corresponding data of the natural products.[7]

To further demonstrate the synthetic potentials of this strategy (Pathway B, Scheme 1), we planned to prepare aryl–dihydronaphthalene-type lignans, such as linoxepin and 7,8-dihydroisojusticidine B, [8] using the cross-coupling reactions. The synthesis started from the APEDA reaction with **13a** and dienophile **41** (Scheme 5), which gave the desired tricyclic core **51** in 76% isolated yield and good enantioselectivity (93% ee). Using similar transformations as preparation of **45**, the desired triflate **52** was obtained through two steps of oxidation and triflation. A Pd(0) catalyzed Suzuki-Miyaura coupling of **52** with aryl boronic acid pinacol ester **53** afforded (–)-7,8-dihydroisojusticidine B (**54**) in 70% yield.[8] The same cross coupling reaction between **52** and **55** worked well to form the desired coupling product **56** in 60% yield. To build the strained dihydrooxepine ring, we first performed the acid-mediated removal of the TBS and two methyl groups, then an intramolecular Mitsunobu reaction was applied to close the seven-membered cyclo-ether D ring. After introduction of an additional methyl group, the total synthesis of (+)-linoxepin was accomplished in 40% yield over 2 steps.[8, 15]

Conclusion

In summary, the first asymmetric total synthesis of aryltetralin cyclic ether lignans aglacins A, B and E were achieved based on an asymmetric photoenolization/Diels–Alder (APEDA) reaction. Both enantiomers of aglacins A, B and E were prepared in 13-14 steps, which enable us to revise the absolute configuration of these natural lignans. The APEDA reaction, between electron-rich 2-methylbenzaldehyde and unsaturated γ-lactone, provided a new approach to rapidly construct the basic tricyclic core of aryltetralin lactone lignans. This strategy was also applied to prepare naturally occurring aryl–dihydronaphthalene-type lignans (–)-7,8-dihydroisojusticidine B and (+)-linoxepin in four and six steps, as well as 27 members of natural product-like molecules bearing a quaternary center at C-8'. We are currently exploring the biological functions and SAR studies of the synthetic aglacins and small-molecule library, which will be disclosed in due course.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: lignans, aglacin, natural products, total synthesis, APEDA reaction

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Natural Product Synthesis

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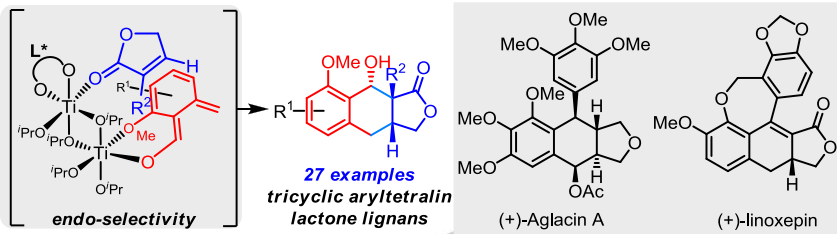
Asymmetric Total Synthesis of Aglacins A, B and E



Asymmetric photoenolization/Diels-Alder reaction (APEDA reaction)

Asymmetric Total Synthesis

Absolute Configuration Revision

We report herein the first asymmetric total synthesis of aryltetralin cyclic ether lignans aglacins A, B and E, based on a novel asymmetric photoenolization/Diels–Alder (APEDA) reaction. This work also enables us: 1) revise the absolute configuration of aglacins; 2) prepare aryl–dihydronaphthalene-type lignans (–)-7,8-dihydro-isojusticidine B and (+)-linoxepin; 3) build a small library of lignans (27 members).