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Divergent Asymmetric Syntheses of Podophyllotoxin and Related Family Members via Stereoselective Reductive Ni-Catalysis

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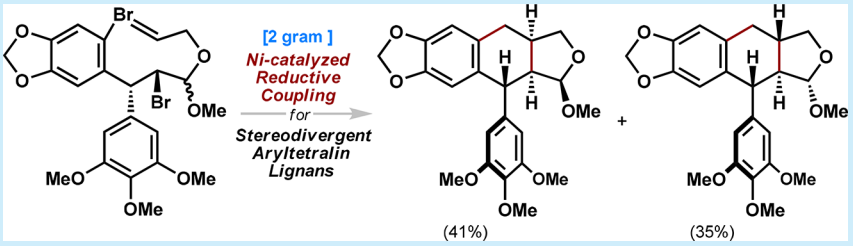
Supporting Information

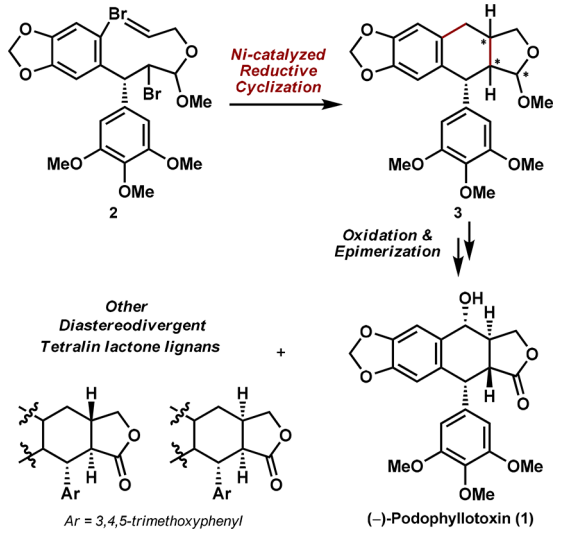


ABSTRACT: A nickel-catalyzed reductive cascade approach to the efficient construction of diastereodivergent cores embedded in *podophyllum* lignans is developed for the first time. Their gram-scale access paved the way for unified syntheses of naturally occurring podophyllotoxin and other members.

While recent years have witnessed impressive developments in the area of nickel-catalyzed reductive coupling,[1] this carbon−carbon formation method has not yet successfully been applied within the context of natural product synthesis. Moreover, the state-of-the art in this field has mainly concerned intermolecular couplings,[2] while less attention was paid to fully intramolecular reactions[3] and stereocontrolled tandem cyclizations, which our group focused on.[4] Further demonstration of the total synthesis of bioactive natural products and pharmaceuticals still remains elusive and, thus, is in high demand.[5]

Podophyllotoxin [PT (**1**), Scheme 1], as a representative aryltetralin lignan[6] of the *podophyllum* family, has received widespread attention from the research community. This molecule can be used for the treatment of angogenital warts, and its derivatives have also been used as chemotherapy drugs, such as etoposide and teniposide for leukemia, lung, and testicular cancer.[7] Historically, PT molecules featuring strained *trans*-ring fusion, four contiguous chiral centers, and an axially locked C9-aryl substituent had been a challenging target. Some total syntheses of PT have been reported so far,[8,9] continuously inspiring innovative tactics developments. Herein, we devised a new and concise route to **1**. First, a Ni-catalyzed reductive cascade of dibromide **2** would lead to the generation of tetrahydronaphtho[2,3-*c*]furan (tetrahydronaphtho = THN) core **3** embedded in this kind of lignans. Formation of diastereodivergent products in such a single operation for the construction of two C−C bonds is a desired goal,[10] therefore enabling access to any members of the *podophyllum* family in principle. Followed by the subsequent regioselective C−H bond oxidation, this class of tetralin lactone lignans, including **1** with four contiguous chiral centers, would be synthesized efficiently.

Scheme 1. Reductive Cyclization Logic to Podophyllotoxin



Our synthesis commenced with commercially available 6-bromopiperonal (Scheme 2). The elongation of its carbon chain was carried out through Horner−Wadsworth−Emmons (HWE) olefination with triethyl phosphonoacetate, and the generated ester could be converted into the corresponding acyl chloride by saponification and the next reaction with pivaloyl chloride. The next stage was the introduction of a chiral auxiliary, which was completed by a condensation between the resulting acyl chloride and (*S*)-4-phenyl-2-oxazolidinone in 10 g scale and a good

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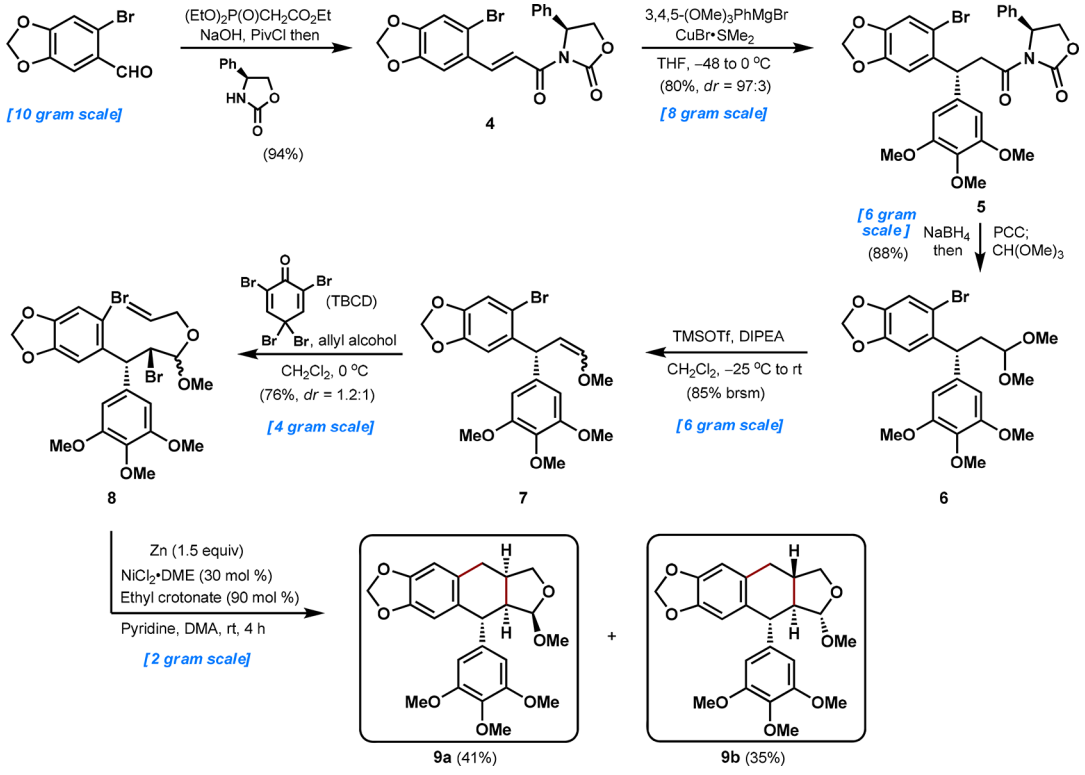
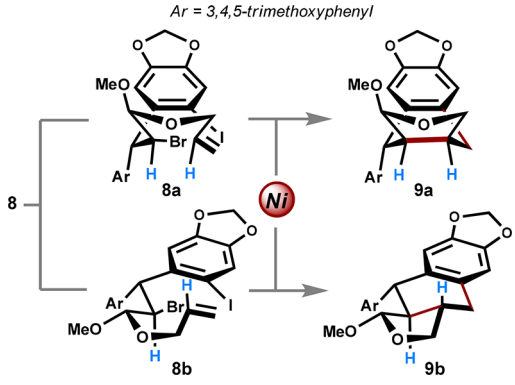
Scheme 2. Gram-Scale Syntheses of Stereodivergent Cores in *Podophyllum* Lignans



overall yield. The crucial asymmetric conjugate addition reaction[11] was achieved by subjection of an arylcopper(I) reagent in situ generated from (3,4,5-trimethoxyphenyl)-magnesium bromide to the above α,β-unsaturated acyl oxazolidinone **4**, with excellent diastereocontrol (**5**, dr = 97:3) and 80% yield. This remote chirality-controlled transformation could be scaled up to 8 g without significant loss of the efficiency. More importantly, *ent*-**5** could also be easily obtained, in principle, from similar reactions with (*R*)-4-phenyl-2-oxazolidinone, therefore demonstrating a potentially enantiodivergent feature of this approach for the construction of a diaryl methine center.[12] The chiral auxiliary in **5** was then removed through reduction mediated by $NaBH_4$, and the optical purity of the resulting alcohol **S1** (Supporting Information) was determined as 93% *ee*. The subsequent oxidation and acetalization gave **6** in nearly quantitative yield. Upon exposure of this acetal to a mixture of TMSOTf and DIPEA,[13] β-elimination occurred to provide the enol ether **7** as a *Z*/*E* mixture in 67% (85% brsm) yield. The site-selective bromination at the double bond proved quite challenging. The initial screening experiments with various bromonium reagents (NBS, Br_2, et al.), including BDSB adapted by Snyder,[14] always led to overbromination products, mainly due to reaction on the electron-rich benzene ring. After extensive optimization studies, we were pleased to find that upon treatment of enol ether **7** with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCD)[15] in CH_2Cl_2 at 0 °C, the desired β-bromo acetals **8** were produced as an inseparable mixture in 76% isolated yield under 4 g scale. By slightly modifying the reaction conditions in our relevant studies,[4h] the expected tandem cyclization of **8** proceeded well to give *cis*-THN[2,3-*c*]furan **9a** and *trans*-THN[2,3-*c*]furan **9b**, which could be separated by flash column chromatography. Excellent stereoselectivities in this Ni-catalyzed reductive cyclization[4h] could be attributed to the respective adoption of the pseudoboat conformation (**8a**) and half-chair conformation (**8b**), as shown in Scheme 3. With gram amounts of diastereodivergent **9a** and **9b** in hand, eight natural products in the *podophyllum* family could be synthesized after a series of oxidation events (Scheme 4).

Scheme 3. Rationalization of Stereoselective Cyclization



The conversion of an acetal moiety in **9a** or **9b** to the corresponding lactone was done by initial hydrolysis and subsequent oxidation of the resulting lactol intermediate.[16] (+)-Deoxypicropodophyllin (**10**) and (+)-isodeoxypodophyllotoxin (**11**) were thus obtained, respectively. Both their optical rotation and spectroscopic data (Tables S1 and S2) were consistent with previous reports.[16,17] Epimerization at C9a in **10** under the enolization/quench conditions (LDA, THF, −78 °C then glacial acetic acid)[18] led to cytotoxic (−)-deoxypodophyllotoxin (**12**), whose spectral data (Table S4) and optical rotation were in agreement with the literature as well.[16,19] A single-crystal analysis of **12** further confirmed its structure (Figure 1, left; selected H atoms have been omitted for clarity).

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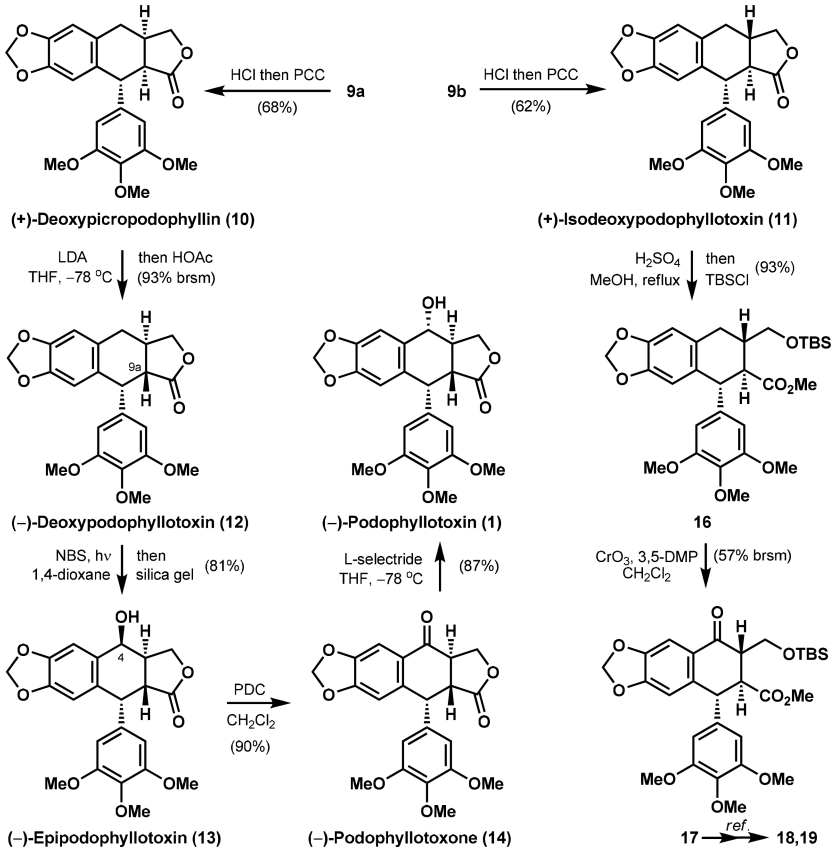
Scheme 4. Divergent Syntheses of Natural Podophyllotoxin and Its Congeners



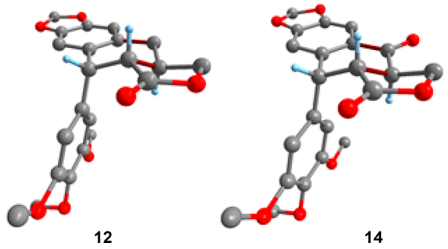


Figure 1. X-ray crystal structures of deoxypodophyllotoxin (left, **12**) and podophyllotoxone (right, **14**).

The next goal was an introduction of C4 hydroxyl, which was expected to be regio- and stereoselective. This formal benzyl C−H oxidation was accomplished in 81% overall yield through radical bromination[20] under visible-light irradiation, followed by the hydrolysis of the resulting labile bromide during column chromatography on silica gel. As shown in Table S5, ^{1}H NMR spectra of the synthetic (−)-epipodophyllotoxin (**13**) were in accord with data reported by Linker.[21] The oxidation of **13** with PDC furnished the synthesis of (−)-podophyllotoxone (**14**),[9g,h] whose absolute stereochemistry was determined by the single-crystal analysis (Figure 1, right; selected H atoms have been omitted for clarity). Upon subjection of **14** to L-selectride in THF at −78 °C, stereospecific reduction of the ketone carbonyl took place to give 87% of natural podophyllotoxin (**1**), and its ^{1}H NMR data (Table S8) were consistent with previous reports.[9e,g] In order to access the corresponding natural products with a higher-oxidation level from **11**, an attempted reaction by a similar operation like that of **12** to **13** was pursued, but surprisingly none of the desired products were observed. The exact reason for this outcome was not clear at present. Eventually, this problem was solved by the ring opening of γ-lactone and the oxidation sequence (right side in Scheme 4). In this regard, treatment of all *trans*-THN[2,3-*c*]furanone **11** with H_2SO_4 (1 N) in reflux MeOH provided γ-hydroxyl ester **15** (not shown), which could be converted into silyl ether **16** by the protection of TBSCl in 93% overall yield. The ketone **17** was thus generated through a regioselective benzyl oxidation[22] with a mixture of 3,5-dimethylpyrazole and CrO_3.[23] Since ketoester **17** was a known compound (Table S9) in the previous synthesis of (−)-picropodophyllin (**18**) and (−)-picropodophyllone (**19**) by Meyers,[9a] the demonstrated route here also constituted a formal synthesis for these two natural products.

In summary, we have developed a nickel-catalyzed fully intramolecular reductive coupling method for the sequential construction of C−C bonds in stereodivergent THN[2,3-*c*]furan scaffolds of antineoplastic aryltetralin lactone lignans. In particular, this tandem cyclization led to expeditious syntheses of several closely related *podophyllum* members, including naturally occurring podophyllotoxin.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00408.

Experimental procedures, characterization data (PDF)
Copies of ^{1}H/^{13}C NMR (PDF)

Accession Codes

CCDC 1811057−1811058 contain the supplementary crystallographic data for this paper. These data can be obtained free of

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charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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