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Ni-Catalyzed Intramolecular Reductive 1,2-Dicarbofunctionalization of Alkene: Facile Access to *Podophyllum* Lignans Core

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In memory of Prof. Xuan Tian

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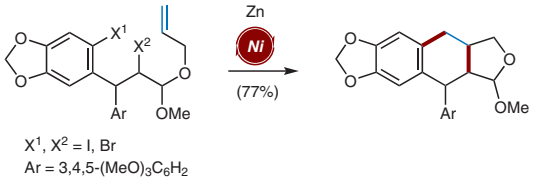

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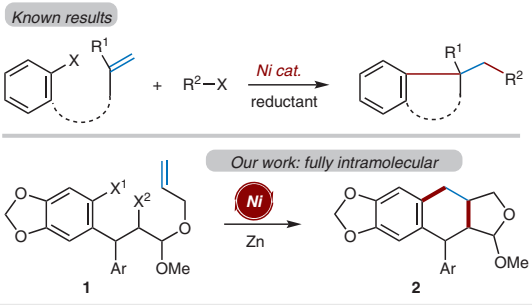
Abstract The facile access to the tetracyclic skeleton of podophyllotoxin, a medicinally important lignan natural product, was efficiently achieved via a unique intramolecular alkylarylation of the tethered alkene in a dihalide under mild conditions using reductive nickel catalysis.

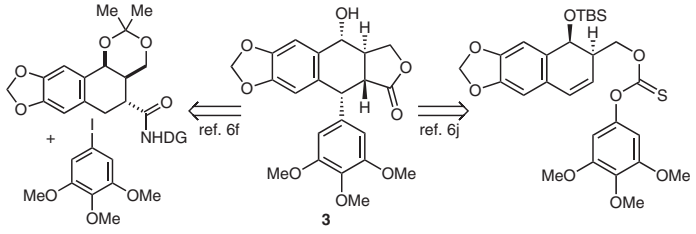
Key words nickel, reductive coupling, intramolecular, cyclization, synthesis

Over the past decade, reductive cross-electrophile couplings catalyzed by nickel complex have evolved into a versatile method for the formation of carbon–carbon bonds under the mild conditions.[1] Notably, recent progress towards reductive 1,2-dicarbofunctionalization of alkenes received more attentions because two vicinal C–C bonds across unactivated or electronically biased olefins could be installed simultaneously by this strategy.[2] As shown in Scheme 1 (top), an aromatic halide with a olefin side chain will cyclize first, then followed by the interception of another electrophile.[3] Meanwhile, nickel-catalyzed intermolecular three-component dicarbofunctionalization reactions under reductive conditions appeared as well.[4]



Scheme 1 Reductive 1,2-dicarbofunctionalization of alkene by Ni-catalysis: state of the art

We were earlier involved in the field of reductive coupling trigger by nickel complex.[5] In particular, our interests focused on the undeveloped area: fully intramolecular reactions and their synthetic applications for total synthesis of bioactive natural products and pharmaceuticals.[5a,d,5f–i] In this work, a dihalide **1** bearing a double bond in the molecule was designed (Scheme 1, bottom), and a tandem cyclization across this double bond would occur to deliver a tetracyclic skeleton **2** embedded in *Podophyllum* lignans through a single operation. As a representative member of this family, podophyllotoxin (**3**, Scheme 2) has been used for the treatment of angogenital warts. Its sugar derivatives



Scheme 2 Selected previous synthesis for podophyllotoxin (**3**)

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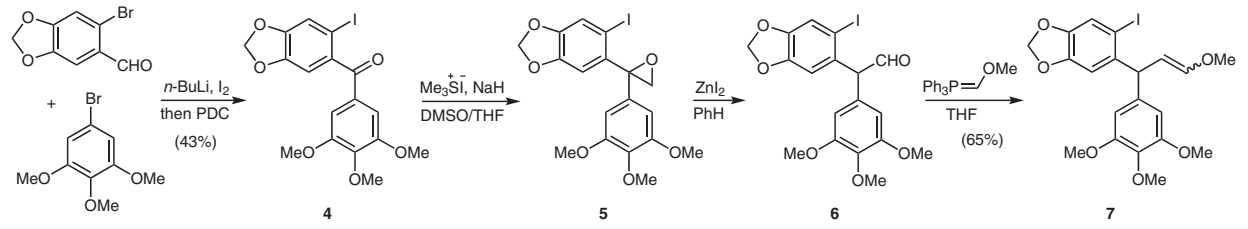
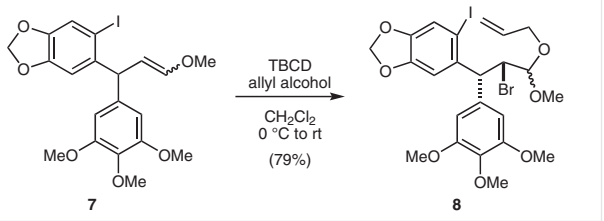


Scheme 3 Preparation of enol ether **7**: a diaryl ketone-based approach

have also been developed as chemotherapy drugs. The described transformation herein was thus very valuable for a rapid access to the core structure of this medicinally important molecule.[6] Especially, several radical cyclzation-based routes had been reported.[6j,t]

The precursor for this fully intramolecular 1,2-dicarbofunctionalization of alkene was prepared according to the synthetic route demonstrated in Scheme 3 and Scheme 4. Firstly, an aryl lithium reagent derived from easily synthesized 3,4,5-trimethoxyl bromobenzene[5f] was added into a solution of commercially available 6-bromopiperonal. The generated diaryl carbinol was then converted into the corresponding iodide via Br–Li exchange protocol. Through an oxidative reaction mediated with pyridinium dichromate (PDC), the desired diaryl ketone **4** was thus obtained in 43% overall yield. Next, one-carbon homologation of ketone **4** was carried out. The initial epoxidation proceeded smoothly under Corey–Chaykovsky reaction conditions, and the resulting epoxide **5** could further rearrange to diaryl acetaldehyde **6** under ZnI_2.[7] Upon subjection of this labile aldehyde to the ylide, which was generated in situ from (methoxylmethyl)triphenylphosphonium chloride,[8] the enol methylether **7** was produced accordingly in 65% overall yield. Notably, only one flash column chromatography was necessary during the conversion of the ketone **4** into **7**.

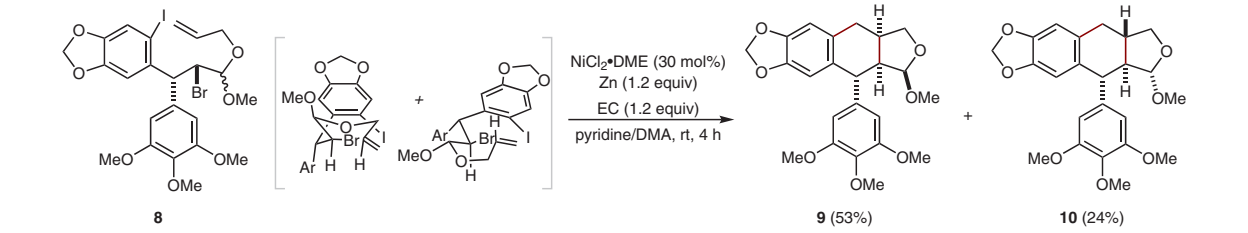


Scheme 4 Preparation of β-bromo acetal as a bicyclization precursor

With sufficient amounts of enol ether **7** in hand, the synthesis of β-bromo acetals **8** was pursued. This seeming routine task proved to be challenging, which was partly attributed to a competitive bromination on the electron-rich benzene ring. After extensive experiments with various reagents, such as Br_2 and NBS, it was found that the employment of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCD)[9] afforded a fairly good regioselectivity, providing β-bromo acetals **8** as a mixture of diastereomers in 79% yield (Scheme 4).[10]

The stage was then set for the intramolecular 1,2-alkylarylation of alkene **8**. Ethyl crotonate (EC), which played a critical role in our previous studies,[5i] was still found to be a best ligand for this fully intramolecular coupling under reductive conditions (Scheme 5). Two separable products **9** and **10** with the core of *Podophyllum* lignans were obtained in a combined yield of 77%. As shown in the Supporting Information, the relative stereochemistries of these two diastereomers were assigned by ^1H–^1H COSY and NOESY spectra, respectively. The typical tetralin structure embedded in **9** and **10** paves the way for the stereodivergent synthesis of this family of natural products.[5h,11]

In summary, a diaryl ketone based approach for the synthesis of enol ether **7** was developed, which secured the supply for the designed bicyclization precursor **8**. This bromoiodide under reductive nickel catalysis constructed two vicinal C(sp^3)–C(sp^3) and C(sp^3)–C(sp^2) bonds across the tethered alkene, therefore establishing the core of podophyllotoxin as a therapeutic agent. We believed that this fully intramolecular conjunctive cross-coupling would find new utilities in the context of natural products synthesis.



Scheme 5 Stereoselective synthesis of tetracyclic skeleton embedded *Podophyllum* lignans

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707188.

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(10) In a 100 mL round-bottom flask, enol ether **7** (1.50 g, 3.1 mmol) was dissolved in anhydrous CH_2Cl_2 (35 mL) and cooled to 0 °C. To this solution was added TBCD (97%, 1.57 g, 3.7 mmol, 1.2 equiv) portionwise, and the mixture was stirred for 30 min at 0 °C. A solution of allyl alcohol (3.6 mL, 62 mmol, 20.0 equiv) in CH_2Cl_2 (5 mL) was then added dropwise, and the resulting mixture was gradually warmed to room temperature and stirred further for 9 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL), Na_2SO_3 (3 mL), and stirred further for 30 min. The resulting mixture was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed with water (2 × 15 mL) and brine (15 mL), respectively, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc = 10:1 → petroleum ether/EtOAc = 4:1) on silica gel to afford **8** (1.519 g, 79% yield) as a yellow oil. R_f = 0.36 (petroleum ether/EtOAc = 2:1). IR (film): ν_{max} = 2930, 2838, 1590, 1504, 1479, 1461, 1422, 1383, 1326, 1265, 1229, 1128, 1037, 929, 845, 792, 736, 701, 685, 582 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (major isomer) = 7.19 (s, 1 H), 6.99 (s, 1 H), 6.52 (s, 2 H), 5.93 (s, 1 H), 5.89 (s, 1 H), 5.86–5.80 (m, 1 H), 5.35 (dd, *J* = 17.2, 1.6 Hz, 1 H), 5.13 (dd, *J* = 10.8, 1.6 Hz, 1 H), 4.76 (d, *J* = 10.8 Hz, 1 H), 4.55 (dd, *J* = 11.2, 2.8 Hz, 1 H), 4.26 (dd, *J* = 13.2, 4.8 Hz, 1 H), 4.00 (d, *J* = 2.4 Hz, 1 H), 3.88 (dd, *J* = 12.8, 5.2 Hz, 1 H), 3.76 (s, 6 H), 3.74 (s, 3 H), 3.31 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3 (2 C), 148.7, 147.3, 137.23, 137.17, 135.6, 133.8, 119.0, 116.7, 107.0, 105.3 (2 C), 102.0, 101.8, 90.5, 69.7, 60.8, 57.7, 57.3, 56.21 (2 C), 56.17 ppm. HRMS (ESI): *m/z* calcd for $C_{23}H_{26}O_7{}^{79}BrINa^+$ [M + Na]$^+$: 642.9799; found: 642.9791.

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