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Pseudo-domino palladium-catalyzed allylic alkylation/Mizoroki–Heck coupling reaction: a key sequence toward (±)-podophyllotoxin

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Abstract

A formal synthesis of podophyllotoxin was carried out in nine steps. The key pseudo-domino step was accomplished through the succession of an intermolecular palladium-catalyzed allylic alkylation and an intramolecular Mizoroki–Heck coupling reaction.

Keywords: Podophyllotoxin; Catalysis; Domino; Palladium; Ring-closure

Podophyllotoxin (Fig. 1), the parent member of the aryltetralin lignan lactone family[1] was first isolated in 1880 from podophyllin,[2] a resinous powder obtained by precipitating an alcoholic tincture of the American Mayapple rhizome (*Podophyllum peltatum*). Although the medicinal properties of podophyllotoxin have been known for thousands of years, particular attention toward this molecule arose from the discovery of its antimitotic activity[3] as a result of its high affinity for tubulin.[4] While altering cellular division during mitosis, podophyllotoxin triggers cellular death.[5] However, the use of this molecule as anticancer agent is hampered due to its high toxicity associated with numerous secondary effects such as nausea, diarrhea, vomiting, and injury of healthy tissues.[6] Consequently, several hemi-synthetic derivatives of podophyllotoxin, such as etoposide[7] and teniposide[8] have been developed and successfully used for the clinical treatment of several cancers, including small cell lung carcinoma, testicular cancer and Kaposi's sarcoma.[9] Interestingly, and in contrast to podophyllotoxin, these analogs do not inhibit tubulin polymerization, but act as topoisomerase II inhibitors, a nuclear enzyme involved in transitional breaks of DNA double-strand, compulsory for transcription.[10]

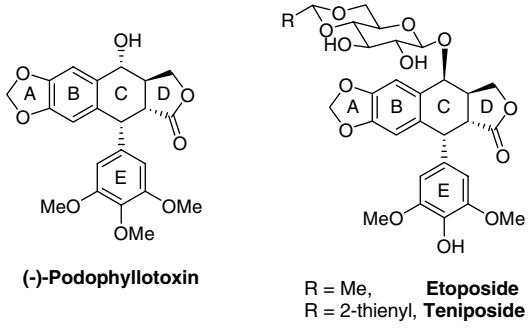

Fig. 1. (−)-Podophyllotoxin, etoposide, and teniposide structures.

In 1998, we reported a stereoselective approach toward 3,4-disubstituted γ-lactams based on the intramolecular palladium-catalyzed allylic alkylation of stabilized acetamide enolate anions taking place exclusively via a 5-*exo* mode of cyclization.[11] A few years later, we disclosed the

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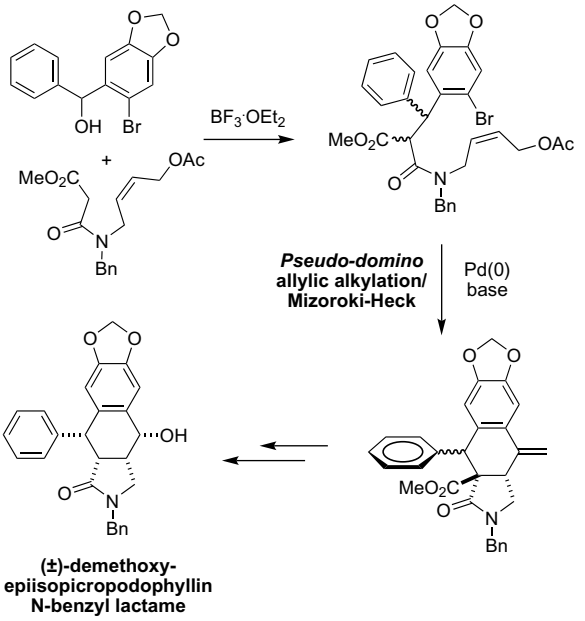
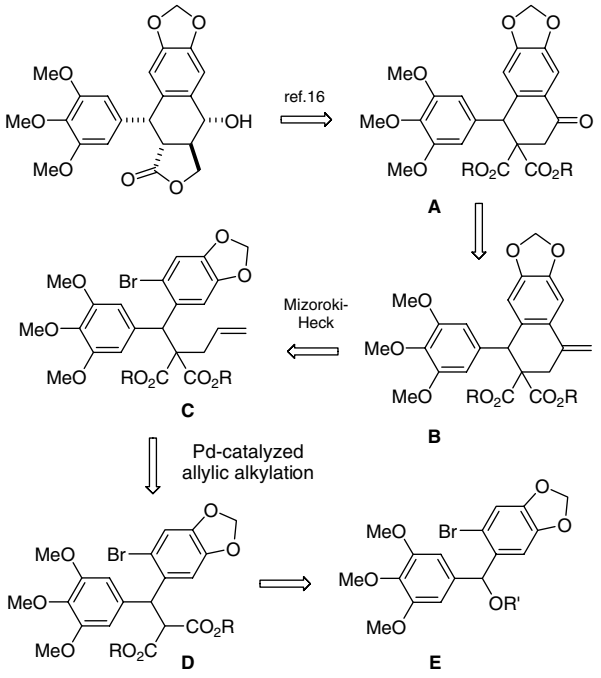


Scheme 1. Synthesis of an aza-analog of podophyllotoxin.[13]

synthesis of a novel aza-analog of podophyllotoxin exploiting a pseudo-domino[12] palladium-catalyzed intramolecular allylic alkylation/Mizoroki–Heck sequence,[13] the cyclization precursor being assembled through an acid-mediated benzhydrylation protocol, previously discovered in our group (Scheme 1).[14]

From this result, we next envisioned to exploit the pseudo-domino palladium-catalyzed allylic alkylation/Mizoroki–Heck sequence process for the synthesis of the parent member, podophyllotoxin.[15]



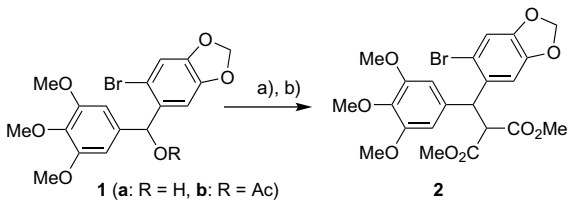
Scheme 2. Retrosynthetic approach to podophyllotoxin.

As two efficient syntheses of aryltetralin lignan lactones reported in the literature entail keto diester **A** as an advanced intermediate,[16] we focused on the latter structure as our synthetic goal. We report herein a formal synthesis of (±)-podophyllotoxin according to the retrosynthetic path depicted in Scheme 2. Key precursor **A** would arise via oxidative cleavage of tetracyclic diester **B**, which could in turn derive from an intramolecular palladium-catalyzed Mizoroki–Heck coupling reaction of the bromoaryl alkene **C**. A palladium-catalyzed allylation may then allow the preparation of **C** from **D**. Finally, alkylation of a malonate diester with the suitably functionalized benzhydrol **E** concludes the retrosynthesis.

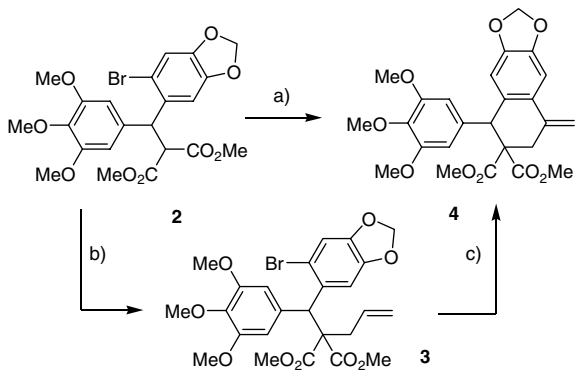
Accordingly, Lewis acid promoted benzhydrylation of dimethyl malonate with benzhydrol **1a**[17] was first attempted (Scheme 3). Neither $BF_3{\cdot}OEt_2$ nor $TiCl_4$ proved to be successful in generating the desired adduct **2**. After some experimentation, **2** could be cleanly obtained (86% yield) by treatment of dimethyl malonate with the benzhydryl acetate **1b** in the presence of $TiCl_4$ in toluene at room temperature.[18]

Intermolecular palladium-catalyzed allylic alkylation of diester **2** was next studied (Scheme 4). Treatment of **2** with allyl acetate (2.5 equiv) in presence of the catalytic system [$Pd(OAc)_2$ (10 mol %), dppe (20 mol %)], NaH as the base (1.2 equiv) in DMF gave, after 2 h at room temperature the allylated diester **3** in 92% yield.[19]

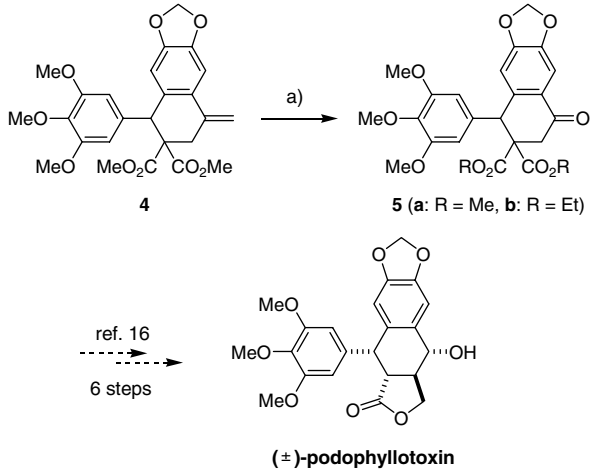
Then, exposure of **3** to the identical catalytic system as previously used in the allylation step [$Pd(OAc)_2$ (10 mol %), dppe (20 mol %)], in the presence of *n*-Bu_4NOAc (2 equiv) in DMF afforded, after 2 h at 100 °C, the expected cyclized product **4** in 93% yield.[20] These two successful experiments occurring under similar reaction conditions prompted us to investigate the one-pot pseudo-domino palladium-catalyzed allylic alkylation/Mizoroki–Heck sequence. In the event, treatment of precursor **2** with $Pd(OAc)_2$ (10 mol %), dppe (20 mol %), NaH (1.2 equiv), allyl acetate (2.5 equiv) and *n*-Bu_4NOAc (2 equiv) in DMF gave, after 2 h at 100 °C, the product of domino reaction **4** in 65% yield.[21,22] Oxidative cleavage of the vinylidene moiety to give ketone **5a** completed the formal synthesis of podophyllotoxin (Scheme 5). This was obtained via osmium-catalyzed *cis*-dihydroxylation of **4** followed by periodate mediated cleavage of the crude diol (75% yield).[23] Compound **5a** was thus obtained in four steps and 42%



Scheme 3. Reagents and conditions: (a) Ac_2O (1.2 equiv), Et_3N (1.2 equiv), DMAP cat., CH_2Cl_2, rt, 1 h, quantitative yield; (b) dimethylmalonate (2 equiv), $TiCl_4$ (1.2 equiv), toluene, 0 °C then rt, 16 h, 86%.



Scheme 4. Reagents and conditions: (a) $Pd(OAc)_2$ (10 mol %), dppe (20 mol %), *n*-Bu_4NOAc (2 equiv), NaH (1.2 equiv), allyl acetate (2.5 equiv), DMF, 100 °C, 2 h, 65%; (b) $Pd(OAc)_2$ (10 mol %), dppe (20 mol %), NaH (1.2 equiv), allyl acetate (2.5 equiv), DMF, rt, 2 h, 92%; (c) $Pd(OAc)_2$ (10 mol %), dppe (20 mol %), *n*-Bu_4NOAc (2 equiv), DMF, 100 °C, 2 h, 93%.



Scheme 5. Reagents and conditions: (a) (i) NMO (2 equiv), $OsCl_3$ (5 mol %) THF/H_2O (9/1), rt, 16 h; (ii) $NaIO_4$ (3 equiv), acetone/H_2O (6/4), rt, 16 h, 75%.

overall yield (pseudo-domino version), or five steps and 56% overall yield (sequential version), starting from benzhydrol **1a**, dimethyl malonate, and allyl acetate. This new route may be regarded as a valid alternative to the previously reported synthesis of **5b**.[16]

In summary, the above described sequence represents a successful nine-step formal synthesis of podophyllotoxin. The key pseudo-domino step was accomplished through the succession of an intermolecular palladium-catalyzed allylic alkylation and an intramolecular Mizoroki–Heck coupling. Extension of the present strategy to the preparation of other aryltetralin lignan lactones is currently underway.

Acknowledgments

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17. See Ref. 15e.
18. *Experimental procedure for the benzhydrylation reaction*: To a solution of benzhydryl acetate **1b** (520 mg, 1.18 mmol, 1 equiv) in toluene (10 mL) were added, under argon atmosphere, at 0 °C dimethylmalonate (270 μL, 2.37 mmol, 1 equiv) and $TiCl_4$ (155 μL, 1.42 mmol, 1.2 equiv). The resulting solution was allowed to warm up slowly to room temperature and stirred overnight before a solution of saturated aqueous $NaHCO_3$ and CH_2Cl_2 were added. The separated aqueous layer was extracted with CH_2Cl_2 and the collected organic layer dried over $MgSO_4$. Solvents were removed under reduced pressure and the crude material purified by flash column chromatography (cyclohexane/ethyl acetate 8/2) to afford **2** in 86% yield as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz): 3.61 (s, 3H), 3.63 (s, 3H), 3.79 (s, 3H), 3.83 (s, 6H), 4.24 (d, $J = 12.4$ Hz, 1H), 5.25 (d, $J = 12.4$ Hz, 1H), 5.93 (d, $J = 1.3$ Hz, 1H), 5.96 (d, $J = 1.3$ Hz, 1H), 6.53 (s, 2H), 6.80 (s, 1H), 7.00 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 48.6, 52.9, 56.2, 57.1, 60.8, 101.9, 104.7, 107.3, 113.3, 115.1, 133.3, 135.7, 137.0, 147.2, 147.7, 153.2, 167.5.
19. *Experimental procedure for the allylic alkylation*: To a solution of $Pd(OAc)_2$ (10 mol %) in dry DMF (500 μL) under nitrogen atmosphere was added dppe (20 mol %). In a separate flask, to a solution of diester **2** (50 mg, 0.1 mmol) in dry DMF (1 mL) at 0 °C under nitrogen atmosphere was added NaH (60% in oil, 0.117 mmol, 1.2 equiv). The resulting mixture was stirred at 0 °C for 15 min and, after warming to room temperature, added to the reaction vessel containing the catalytic system. Allyl acetate (27 μL, 0.244 mmol, 2.5 equiv) was then added and the resulting mixture was stirred at room temperature for 2 h. A saturated aqueous NH_4Cl solution was added and the aqueous phase was extracted three times with Et_2O. The collected organic phases were washed three times with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by flash chromatography (cyclohexane/ethyl acetate 8/2) to afford **3** (92%). ^{1}H NMR ($CDCl_3$, 400 MHz): 2.72–2.90 (2dd, $J = 14.2$, 7.1 Hz, *AB* system, 2H), 3.55 (s, 3H), 3.63 (s, 3H), 3.79 (s, 3H), 3.80 (s, 6H), 4.95 (d, $J = 16.9$ Hz, 1H), 5.00 (d, $J = 10.1$ Hz, 1H), 5.31 (s, 1H), 5.53–5.63 (m, 1H), 5.96 (d, $J = 1.0$ Hz, 1H), 5.98 (d, $J = 1.0$ Hz, 1H), 6.64 (s, 2H), 7.00 (s, 1H), 7.42 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 40.5, 52.1, 52.3, 52.9, 56.0, 60.7, 63.4, 101.8, 107.3, 109.4, 113.0, 116.7, 119.1, 132.4, 132.6, 134.7, 136.7, 146.9, 147.3, 152.4, 170.7, 171.2.
20. *Experimental procedure for the Mizoroki–Heck coupling reaction*: To a solution of $Pd(OAc)_2$ (10 mol %) in dry DMF (2 mL) under nitrogen atmosphere were added dppe (20 mol %), tetra-*n*-butyl ammonium acetate (181 mg, 0.60 mmol, 2 equiv) and a DMF solution (2 mL) of **3** (166 mg, 0.30 mmol). The resulting mixture was stirred at 100 °C for 2 h. Then, a saturated aqueous NH_4Cl solution was added and the aqueous phase was extracted three times with Et_2O. The collected organic phases were washed three times with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by flash chromatography (cyclohexane/ethyl acetate 8/2) to afford cyclic diester **4** (93%). ^{1}H NMR ($CDCl_3$, 400 MHz): 2.95–3.22 (2d, $J = 15.1$ Hz, *AB* system, 2H), 3.58 (s, 3H), 3.66 (s, 3H), 3.73 (s, 6H), 3.79 (s, 3H), 4.82 (s, 1H), 5.02 (d, $J = 1.5$ Hz, 1H), 5.46 (d, $J = 1.5$ Hz, 1H), 5.89 (d, $J = 1.2$ Hz, 1H), 5.92 (d, $J = 1.2$ Hz, 1H), 6.22 (s, 2H), 6.46 (s, 1H), 7.08 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 33.0, 49.6, 52.4, 52.9, 56.0, 59.3, 60.8, 101.1, 102.9, 107.0, 109.4, 110.1, 126.8, 131.3, 136.0, 137.2, 138.1, 147.1, 148.3, 152.8, 169.7, 170.6.
21. Although the yield of this step (65%) is somewhat lower to the calculated global yield of the two separated steps (86%), the success of the pseudo-domino sequence represents an interesting goal from the conceptual (as it validates the feasibility of the principle) as well as practical viewpoint (as it saves a work-up procedure and a purification step).
22. *Experimental procedure for the allylic alkylation/Mizoroki–Heck coupling pseudo-domino process*: To a solution of $Pd(OAc)_2$ (10 mol %) in dry DMF (500 μL) under nitrogen atmosphere was added dppe (20 mol %). After 5 min stirring allyl acetate (27 μL, 0.244 mmol, 2.5 equiv), then tetra-*n*-butyl ammonium acetate (60 mg, 0.20 mmol, 2 equiv) were added. In a separate flask, to a solution of diester **2** (50 mg, 0.1 mmol) in dry DMF (1.5 mL) at 0 °C under nitrogen atmosphere was added NaH (60% in oil, 0.117 mmol, 1.2 equiv). The resulting mixture was stirred at 0 °C for 15 min and, after warming to room temperature, added to the reaction vessel containing the catalytic system. After stirring at 100 °C for 2 h, a saturated aqueous NH_4Cl solution was added and the aqueous phase was extracted three times with Et_2O. The collected organic phases were washed three times with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by flash chromatography (cyclohexane/ethyl acetate 8/2) to afford cyclic diester **4** in 65% yield.
23. *Experimental procedure for the oxidative cleavage*: To a solution of **4** (87 mg, 0.185 mmol, 1 equiv) in THF/H_2O (4.5 mL/0.5 mL), 4-methylmorpholine-*N*-oxide (51 mg, 0.37 mmol, 2 equiv) and $OsCl_3 \cdot \times H_2O$ (2.75 mg, 5 mol %) were added in this order. The resulting dark suspension was allowed to stir at room temperature overnight. An excess of 50 wt.% aqueous $NaHSO_3$ solution (20 mL) was added and the solution was stirred for further 15 min. The separated aqueous layer was extracted with AcOEt (3 × 10 mL) and solvents were removed under reduced pressure. The resulting crude product was then dissolved in acetone/H_2O (12 mL/8 mL) and $NaIO_4$ (119 mg, 0.56 mmol, 3 equiv) was added in one portion. After stirring for 3 h at room temperature, acetone was removed under reduced pressure, brine was added (10 mL) and the resulting aqueous layer extracted with AcOEt (3 × 10 mL). The organic layer was then dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude material was purified by flash chromatography (cyclohexane/ethyl acetate 6/4) to afford keto diester **5** in 75% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): 3.18–3.30 (2d, $J = 18.2$ Hz, *AB* system, 2H), 3.65 (s, 6H), 3.72 (s, 6H), 3.79 (s, 3H), 5.05 (s, 1H), 6.02 (s, 2H), 6.19 (s, 2H), 6.63 (s, 1H), 7.47 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 38.3, 49.8, 52.9, 53.4, 56.1, 60.0, 60.8, 102.0, 105.5, 106.6, 108.8, 126.3, 132.7, 137.7, 140.3, 147.9, 153.2, 153.4, 168.3, 169.9, 192.8.