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Pd-catalyzed route to (±)-podophyllotoxin skeleton. Synthesis of the aryltetralin derivative

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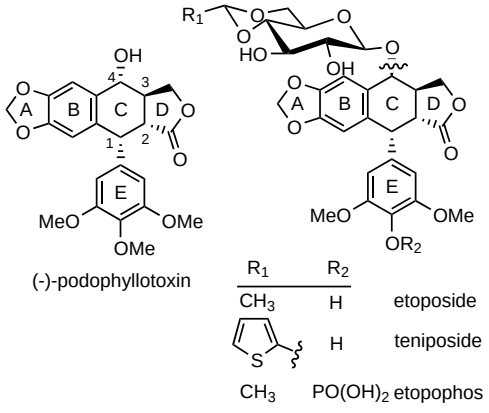
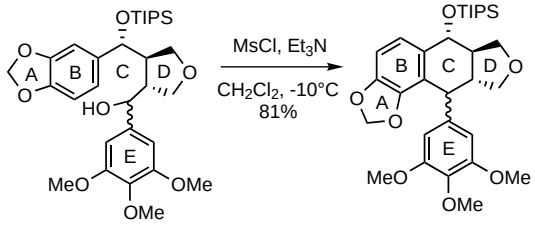
Abstract—A new Pd-catalyzed route to (±)-podophyllotoxin is disclosed. The strategy is based on an efficient organoaqueous reaction that diastereoselectively introduces the C-4 hydroxyl group and the furan ring. Further functionalization led to an iododerivative, which was cyclized under optimized conditions either to the aryltetralin of (±)-podophyllotoxin or to a five-membered ring isomer.

Podophyllotoxin and many closely related lignans are known to have important antineoplastic and antiviral properties.[1] Isolated from *Podophyllum peltatum* and *Podophyllum emodi*, (−)-podophyllotoxin is a potent antimitotic, binding to tubulin and inhibiting microtubule formation. Other congeners such as etoposide,[2] teniposide, etopophos,[3] have recently emerged as promising drug candidates (Scheme 1).

Several racemic and asymmetric syntheses have been described in the literature.[4] Strategies are mainly based on the preparation of either a γ-oxo ester or a dihydroxy acid, on a tandem conjugate addition route or on a Diels–Alder reaction. Berkowitz's group has recently described an original synthesis of (−)-podophyllotoxin, that differs from others in the way that it includes an enzyme-catalyzed asymmetric transformation and the late introduction of the E ring.[5] As part of our ongoing program devoted to Pd-catalyzed reactions in organoaqueous media,[6,7] we have discovered a new reaction named carbohydroxypalladation[8] that creates simultaneously and diastereoselectively carbon–carbon and carbon–oxygen bonds to form a functionalized furan ring. The analogy to the D-ring of (±)-podophyllotoxin including the C-4 hydroxy group prompted us to envisage a new approach for this antitumor molecule. We have reported the synthesis of an analogue based on an unusual regioselectivity in the intramolecular Friedel–Crafts type reaction.[9]



Scheme 1.



We envisaged a new retrosynthetic approach and wish to describe the preparation of (±)-podophyllotoxin aryltetralin skeleton. We decided to introduce the E ring as late as possible via an intermolecular Michael addition (Scheme 2). The aryltetralin intermediate may be prepared via an intramolecular Heck reaction starting from the iodide **3**. Only one example of such a

Keywords: (±)-podophyllotoxin; carbohydroxypalladation; Heck cyclization; aryltetralin; ene-ynes.

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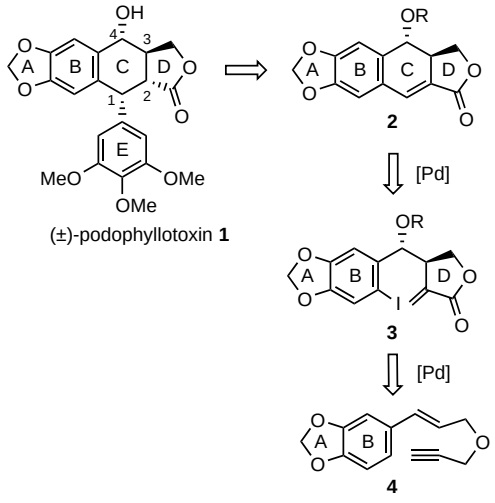


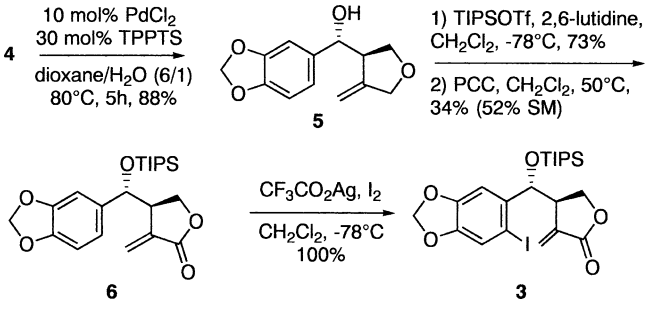
Scheme 2.

reaction was described in the literature for the synthesis of deoxypodophyllotoxin.[10] The functionalized lactone may arise from the propargylether **4** via a carbohydroxypalladation followed by an oxidation and a iodination reaction.

The ether was prepared according to a previously described procedure from piperonal within three steps in 77% yield.[9] The carbohydroxypalladation occurred smoothly using 10 mol% Pd(II) and 30 mol% of TPPTS (tris(*m*-sulfonatophenyl)phosphine trisodium salt) to give the desired alcohol **5** (Scheme 3). The diastereoselectivity was previously confirmed and mechanism is still under investigation.[11] The alcohol was protected with triisopropylsilyltriflate in good yield. The formation of the lactone was directly realized with pyridinium chlorochromate in refluxing dichloromethane in moderate yield.

Starting material (52%) was recovered and recycled. Another method based on two steps (SeO_2/HCO_2H and then MnO_2) gave lower yield and no recovered starting material. The aromatic ring was then smoothly iodided using silver trifluoroacetate and iodine with quantitative yield.[12] The regioselectivity was confirmed by ^1H NMR.[13]

Having the aryltetralin precursor in hand, we then tried the cyclization using numerous Heck conditions. As



Scheme 3.

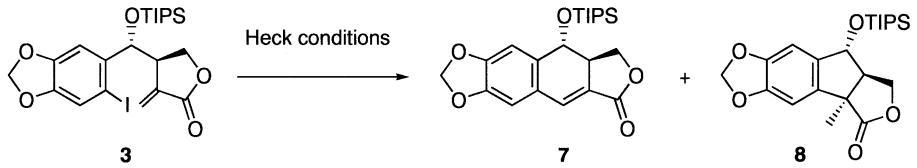
exemplified in Table 1, the smooth organoaqueous conditions Pd(II)/TPPTS[6] (entry 1) or the Jeffery's conditions[14] (entry 2) led to no conversion of the iodide. Total degradation of the iodo compound was observed at higher temperature (entry 3) using the Herrmann and Beller palladacycle.[15] The Heck cyclization conditions used by Ikeda's group[10] for desoxypodophyllotoxin gave a mixture of unseparable compounds (entry 4). Suspecting that K_2CO_3 may produce degradative derivatives, we then switched to organic base. The best result was obtained using a $Pd(OAc)_2/PPh_3$ system in acetonitrile and diisopropylethylamine as the base (entry 5).

Surprisingly, the cyclization did not lead to the expected six-membered ring **7** but to a five-membered ring **8** in 31% isolated yield. We can explain the formation of this cycle via a palladium hydride, that would arise either from β-hydride-elimination on diisopropylethylamine or hydride transfer to a cationic palladium intermediate.[16] We also envisaged to enhance the chemical yield by adding 2 equiv. of thallium salts,[17] known to favor a cationic pathway in the Heck cyclization. As the reaction seemed quite slow, catalytic portion of Pd(II)/L was added until completion at 110°C. We were pleased to detect the desired six-membered ring compound **7** as a 1/1 mixture using K_2CO_3 in acetonitrile (entry 6) even if much degradation was observed by TLC.[18] Changing the base and the ligand had a concomitant influence. The use of pentamethylpiperidine[19] seemed to suppress the degradation of starting material. The selectivity reached 100% in favor of the desired aryltetralin by employing a bidentate ligand, dppe (diphenylphosphinoethane), albeit a 50% conversion (entry 7).[20]

Our next goal was to optimize the conditions by using PMP/TlOAc to favor the six-membered ring formation and a bidentate ligand. We turned our attention to the well-known ferrocene dppf (1.1′-bis-(diphenylphosphino)ferrocene). As documented in Table 2, the reaction conducted in CH_3CN wasn't complete even though the selectivity was as high as with dppe (entry 1 compared to Table 1 entry 7). The conversion reached 100% in toluene, but the stereoselectivity was lower and accompanied with degradation of the iodide detected by TLC (entry 2). The best result was obtained in dioxane using 20 mol% palladium (entry 3). Clean cyclization was observed at 110°C during 23 h and led to the desired aryltetralin with 85% yield.

In conclusion, we have prepared the functionalized aryltetralin moiety of podophyllotoxin via two palladium-catalyzed reactions. The carbohydroxypalladation led diastereoselectively to the concomitant cyclization and hydroxylation to form the functionalized D furan. The second palladium-catalyzed reaction, an intramolecular cyclization, was very sensitive to the substrate, the base and the solvent. Optimized conditions were obtained using bidentate ligand dppf, PMP and thallium as base and additive in dioxane at 110°C. This synthesis constitutes a short and efficient preparation of (±)-podophyllotoxin precursor, that may open a new organometallic route to analogues.

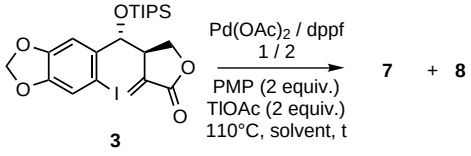
Table 1. Pd-catalyzed Heck reaction of iododerivative **3**



Entry	Pd catalyst (mol%), ligand (mol%)	Solvent	Base (equiv.), additive (equiv.)	T (°C)	t (h)	Isomer **7**	Isomer **8**	Conv. % (yield[a])
1	$PdCl_2$ (10), TPPTS (30)	CH_3CN/H_2O (6/1)	i-Pr_2NEt (5)	80	48	/	/	0[b]
2	$Pd(OAc)_2$ (5), PPh_3 (10)	CH_3CN/H_2O (10/1)	K_2CO_3 (2.5), n-Bu_4NHSO_4 (1)	80	96	/	/	0[b]
3	$Pd_2(\mu\text{-}OAc)_2(P\text{-}(o\text{-tolyl})_3)_2$ (4)	CH_3CN/DMF /H_2O (5/5/1)	n-Bu_4NOAc (2)	120	48	/	/	100[c]
4	$PdCl_2(PPh_3)_2$ (10), PPh_3 (30)	DMF	K_2CO_3 (2)	90	48	/	/	100[c]
5	$Pd(OAc)_2$ (10), PPh_3 (30)	CH_3CN	i-Pr_2NEt (5)	80	48	0	100	100 (31)
6[b]	$Pd(OAc)_2$ (30), PPh_3 (60)	CH_3CN	K_2CO_3 (2), TlOAc (2)	110	26	50	50	100 (25)
7	$Pd(OAc)_2$ (30), dppe (60)	CH_3CN	PMP (2), TlOAc (2)	110	22	100	0	50

[a] Global yield, mixture of isomers **7** and **8**.
[b] Recovered SM.
[c] Degradation of SM.

Table 2. Optimization of the Pd-catalyzed Heck reaction



Entry	[Pd]	Solvent	t (h)	**7**[a]	**8**[a]	Conv. % (yield)
1	20	CH_3CN	17	100	0	50 (n.d.)
2	30	Toluene	21	80	20	100 (49)
3	20	Dioxane	23	100	0	100 (85)

[a] Diastereomeric ratio measured by ^1H NMR.

Acknowledgements

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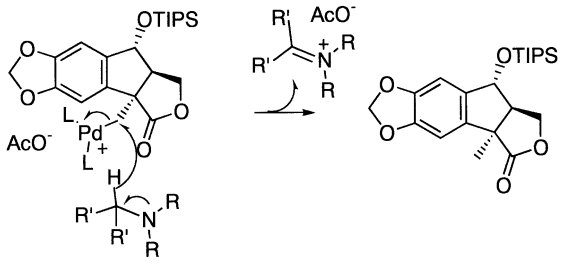
References

1. (a) Ayres, D. C.; Loike, J. D. *Lignans. Chemical, Biological and Clinical Properties*; Cambridge University Press: Cambridge, 1990; Chapters 3 and 4; (b) Jardine, I. *Anticancer Agents Based on Natural Products Models*. Podophyllotoxins. Academic: New York, 1980; pp. 319–351; (c) Imbert, T. F. *Biochimie* **1998**, *80*, 207–222.
2. (a) Imbert, T. F. *Biochimie* **1998**, *80*, 207–222; (b) Damayanthi, Y.; Lown, J. W. *Curr. Med. Chem.* **1998**, *34*, 1514–1521; (c) Meresse, P.; Bertounesque, E.; Imbert, T.; Monneret, C. *Tetrahedron* **1999**, *55*, 12805–12818.
3. De Jong, R. S.; Slijfer, E. A. M.; Uges, D. R. A.; Mulder, N. H.; de Vries, E. G. E. *Br. J. Cancer* **1997**, *76*, 1480–1483.
4. (a) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75–96 and references cited therein; (b) Ward, R. S. *Synthesis* **1992**, 719–730.
5. Berkowitz, D. B.; Choi, S.; Maeng, J.-H. *J. Org. Chem.* **2000**, *65*, 847–860.
6. For reviews, see: (a) Genêt, J. P.; Savignac, M. *J. Organomet. Chem.* **1999**, *490*, 305; (b) Genêt, J. P.; Savignac, M.; Lemaire-Audoire, S. In *IUPAC Monographs Chemistry for the 21st Century*, Murahashi, S.-I.; Davies,

S. G., Eds. Transition Metal Catalysed Reactions. 1999, p. 55.
7. (a) Michelet, V.; Galland, J.-C.; Charruault, L.; Savignac, M.; Genêt, J. P. *Org. Lett.* **2001**, *3*, 2065–2067; (b) Dupuis, C.; Adiey, K.; Charruault, L.; Michelet, V.; Savignac, M.; Genêt, J. P. *Tetrahedron Lett.* **2001**, *42*, 6523–6527.
8. Galland, J. C.; Savignac, M.; Genêt, J. P. *Tetrahedron Lett.* **1997**, *38*, 8695–8699.
9. Galland, J. C.; Diaz, S.; Savignac, M.; Genêt, J. P. *Tetrahedron* **2001**, *57*, 5137–5148.
10. Ishibashi, H.; Ito, K.; Hirano, T.; Tabuchi, M.; Ikeda, M. *Tetrahedron* **1993**, *49*, 4173–4182.
11. (a) Unpublished results; (b) Similar derivatives have been described with Pt(II) catalyst: (a) Mendez, M.; Munoz, M. P.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11549–11550; (b) Mendez, M.; Munoz, M. P.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511–10520.
12. Wilson, C. V.; Jansen, D. E. *Org. Synth.*; Wiley: New York, 1963; Collect. Vol. 4, pp. 547–549.
13. Spectral analysis of iodide **3**: ^{1}H NMR (δ in ppm, $CDCl_3$, 400 MHz): 7.2 (s, 1H); 7.01 (s, 1H); 6.32 (d, 2.4 Hz, 1H); 6.01 (d, 1.3 Hz, 1H); 5.98 (d, 1.3 Hz, 1H); 5.64 (d, 2.4 Hz, 1H); 5.17 (d, 4 Hz, 1H); 4.61 (dd, 3.6 Hz, 9.3 Hz, 1H); 4.17 (dd, 8.4 Hz, 9.1 Hz, 1H); 3.31 (m, 1H); 0.98 (s, 21H). ^{13}C NMR (δ in ppm, $CDCl_3$, 100 MHz): 170.8; 148.9; 148.3; 137.2; 135.9; 118.5; 118.2; 108; 102; 101.6; 79.8; 65.9; 46.4; 19.5; 12.6.
14. Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051–3054.
15. Catalyst used in intramolecular Heck reaction for the (–)-cephalotaxine synthesis: Tietze, L. F.; Schirock, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264–10269.
16. (a) For a recent hydride transfer, see: Lau, S.; Andersen, N.; Keay, B. *Org. Lett.* **2001**, *3*, 181–184; (b) The formation of **8** may be explained via the following intermediate.



17. Grigg, R.; Loganathan, V.; Sukirthalingram, S.; Sridharan, V. *Tetrahedron Lett.* **1990**, *31*, 6573–6576.
18. The starting material and cyclized compounds have closed R_f. The isomeric ratio is measured by ^{1}H NMR. Isolated yields of C-6 and C-5 isomer are given for 100% conversion and 100% selectivity.
19. Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477–6488.
20. For a recent example of intramolecular Heck reaction using dppe, see: Gras, E.; Guillou; Thal, C. *Tetrahedron Lett.* **1999**, *40*, 9243–9244.