

Enantioselective Sequential Conjugate Addition—Allylation Reactions: A Concise Total Synthesis of (+)-Podophyllotoxin

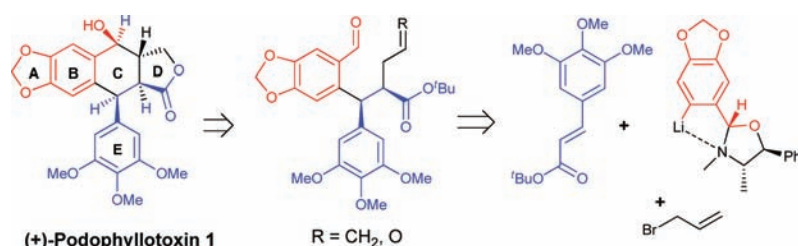
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ABSTRACT



A highly flexible and concise total synthesis of (+)-podophyllotoxin featured with an enantioselective sequential conjugate addition-allylation reaction was reported. Starting from commercially available 3,4,5-trimethoxycinnamic acid, this new route leads to (+)-podophyllotoxin 1 in only eight steps with 29% overall yield.

The natural aryltetralin lactone (+)-podophyllotoxin (**1**) (Figure 1) occupies a unique position among lignans with an intriguing structure (four contiguous chiral centers, rigid trans lactone, pseudoaxial ring E, and facile epimerization at C2 and C4). It has currently been used for the treatment of venereal warts and also served as an important precursor for the preparation of clinical antitumor drugs etoposide and teniposide.¹ A growing demand for podophyllotoxin worldwide has exerted severe pressure on the plant resource.² Owing to its significant clinical role, interesting molecular architecture and the supply issue, development of efficient synthetic routes leading to enantioselective

synthesis of podophyllotoxin retains a target of pursuit for decades.

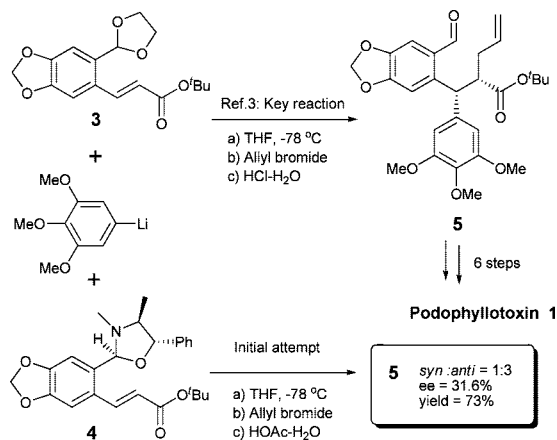
As part of our ongoing program in seeking more efficient and flexible synthetic strategies toward bioactive natural products and its analogues, we recently reported a new route (12 steps) for the synthesis of (±)-podophyllotoxin, with the key reaction being a sequential reaction of aryl lithium conjugate addition coupled with alkylation of allyl bromide toward cinnamic derivative **3** (Scheme 1).³ Dealing with the key reaction in a racemic approach is the major drawback of our previous synthesis. In this paper, we report a highly enantioselective version for the key Michael addition—

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(2) (a) Eyberger, A. L.; Dondapati, R.; Porter, J. R. *J. Nat. Prod.* **2006**, *69*, 1121. (b) Lin, H.-W.; Kwok, K. H.; Doran, P. M. *Biotechnol. Prog.* **2003**, *19*, 1417. (c) Canel, C.; Moraes, R. M.; Dayan, F. E.; Ferreira, D. *Phytochemistry* **2000**, *54*, 115.

(3) Wu, Y.; Zhang, H.; Zhao, Y.; Zhao, J.; Chen, J.; Li, L. *Org. Lett.* **2007**, *9*, 1199.

Scheme 1. Initial Attempts toward Enantioselective Sequential Michael Addition–Alkylation



alkylation process and a concise (eight steps) total synthesis of (+)-podophyllotoxin.

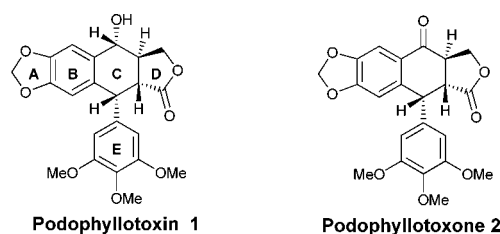


Figure 1. Natural podophyllotoxin and podophyllotoxone.

Our initial plan to address the key Michael addition–alkylation was to utilize protocols developed by Alexakis^{4e} and Frey^{4f} (in both cases, enantiopure pseudoephedrine was used in Michael acceptor both as a protecting group and a chiral auxiliary on the aldehyde motif of cinnamic derivatives, only Michael addition, without the subsequent alkylation, being reported).⁴

Since natural (*S,S*)-(+)-pseudoephedrine was the only available material in hand,⁵ it was then employed to prepare oxazolidine **4**. Although substrates similar to **4** resulted in

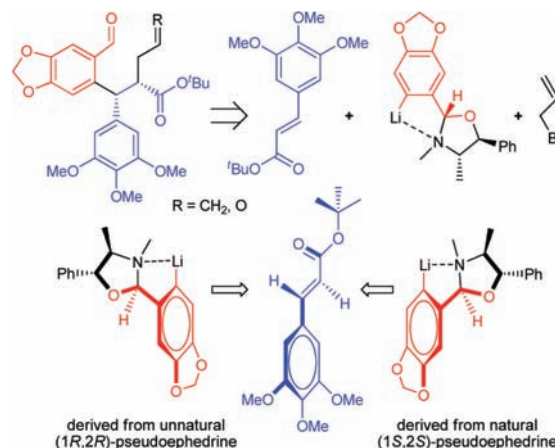
(4) For recent application of ephedrine derivatives in Michael addition, see: (a) Kummer, D. A.; Chain, W. J.; Morales, M. R.; Quiroga, O.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 13231. (b) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badia, D.; Uria, U.; Iza, A. *J. Org. Chem.* **2006**, *71*, 7763. (c) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badia, D.; Iza, A.; Uria, U. *Org. Lett.* **2006**, *8*, 2535. (d) Smitrovich, J. H.; DiMichele, L.; Qu, C.; Boice, G. N.; Nelson, T. D.; Huffman, M. A.; Murry, J. J. *J. Org. Chem.* **2004**, *69*, 1903. (e) Alexakis, A.; Sedrani, R.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 4411. (f) Frey, L. F.; Tillyer, R. D.; Caille, A.-S.; Tschaen, D. M.; Dolling, U.-H.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 3120.

(5) Due to the regulation governing the sale and production of ephedrine and pseudoephedrine in China, we are only able to access natural (+)-ephedrine and natural (+)-pseudoephedrine; we are unable to get unnatural ephedrine and pseudoephedrine, although those two isomers are listed in the Aldrich catalogue.

good enantioselectivities in the literature (ref 4e, f), our substrate failed (Scheme 1), however, with a diastereomeric mixture of compound **5** being obtained. We reckoned that the steric hindrance as well as chelation effects enhanced by the oxazolidine moiety might be the cause of low stereoselectivity.

Having failed to effect the desired conversion, alternative way was thus sought. Carefully analysis of the model of natural pseudoephedrine derived oxazolidine; it was postulated that a chelated chiral aryllithium reagent would favor the formation of diastereoisomer with desired stereochemistry (Scheme 2).

Scheme 2. New Retrosynthetic Analysis of Podophyllotoxin



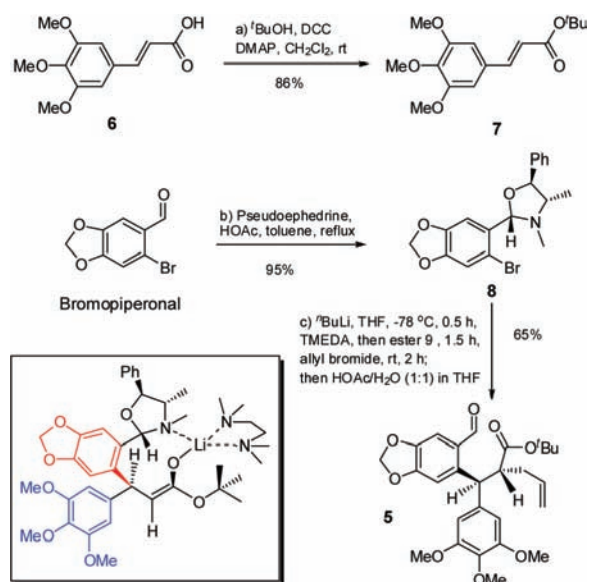
Based on model analysis, unnatural (+)-pseudoephedrine might provided the desired absolute configuration for the synthesis of natural podophyllotoxin. Because we were only able to access natural (+)-pseudoephedrine, we decided to use (+)-pseudoephedrine to confirm the model postulate. 6-Bromopiperonal was therefore treated with (+)-pseudoephedrine and directly converted to oxazolidine **8** as a single diastereomer (Scheme 3).⁶

When oxazolidine-derived aryllithium was used as reagent, conjugate addition–alkylation occurred as expected, and after deprotection with aqueous acetic acid, a diastereomeric mixture (*syn/anti* = 1/11) was obtained in 64% yield with an enantiomeric excess of 84.8% being observed (Chiral HPLC analysis on AD-H column). In order to optimize the stereoselectivity, we decided to add *N,N,N',N'*-tetramethylethylenediamine (TMEDA), a frequently used solvating agent in organolithium chemistry⁷ with observed beneficial effects on stereoselectivity.^{7a} To our delight, addition of TMEDA not only provided excellent diastereoselectivity (with no *syn*-diastereoisomer being detected by NMR, *dr* = 96.8% by Chiral HPLC,

(6) Neelakantan, L. *J. Org. Chem.* **1971**, *36*, 2256.

(7) (a) Agami, C.; Comesse, S.; Kadouri-Puchot, C. *J. Org. Chem.* **2002**, *67*, 1496. (b) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.

Scheme 3. Enantioselective Sequential Michael Addition–Alkylation



see model in Scheme 3) but also improved the enantioselectivity dramatically (the ee value was increased to 98.6%). A 65% yield was obtained in the presence of TMEDA.

In order to get further insight toward the generality of this process, a number of cinnamic derivatives were evaluated under optimized conditions, and good yields and excellent ee were ensured for substrates utilized in this research. The results are summarized in Figure 2. It was worthwhile to note that the (*S,S*)-(+)-pseudoephedrine could be recycled after deprotection of the oxazolidine motif, while this new protocol also provided a good access of pharmaceutically important intermediates such as β,β -diaryl α -alkyl-substituted propionic acid derivatives (see ref 4).

Having established the enantioselective addition–allylation procedure, we turned our attention to the total synthesis of podophyllotoxin. Following our previously established procedure, aldehyde **5** was submitted to an oxidative cleavage followed by an L-proline-mediated adol cyclization and a selective oxidation with MnO_2 to afford intermediate **16**. In our previous synthesis, ketone **16** was transformed to podophyllotoxin via a four-step sequence, a relatively lengthy procedure. We decided to explore a new approach. After the *tert*-butyl ester group being hydrolyzed by treatment with hydrochloric acid in acetonitrile, an esterification with DCC provided (+)-podophyllotoxone in 90% yield ($[\alpha]_{\text{D}}^{27} = +92.9$, c 0.113, CHCl_3).⁸ Selective reduction with L-Selectride⁹ provided

(8) Dewick, P. M.; Jackson, D. E. *Phytochemistry* **1981**, *20*, 2277.

(9) In comparison with $\text{LiAlH}(\text{O}-t\text{-Bu})_3$ used in the literature for the reduction of the ketone moiety in podophyllotoxone, L-Selectride provided better yields and selectivity.

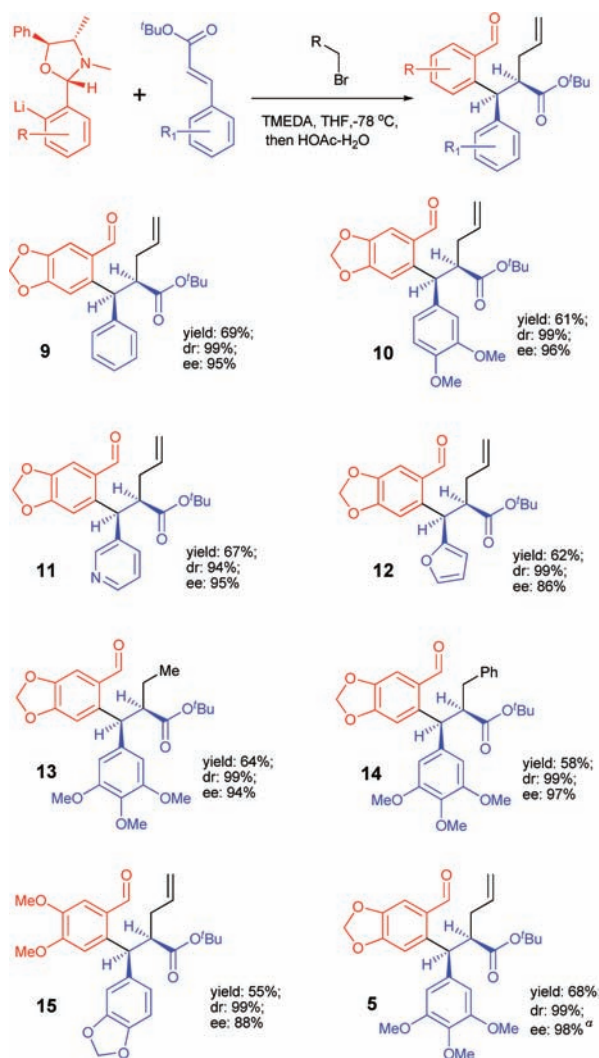
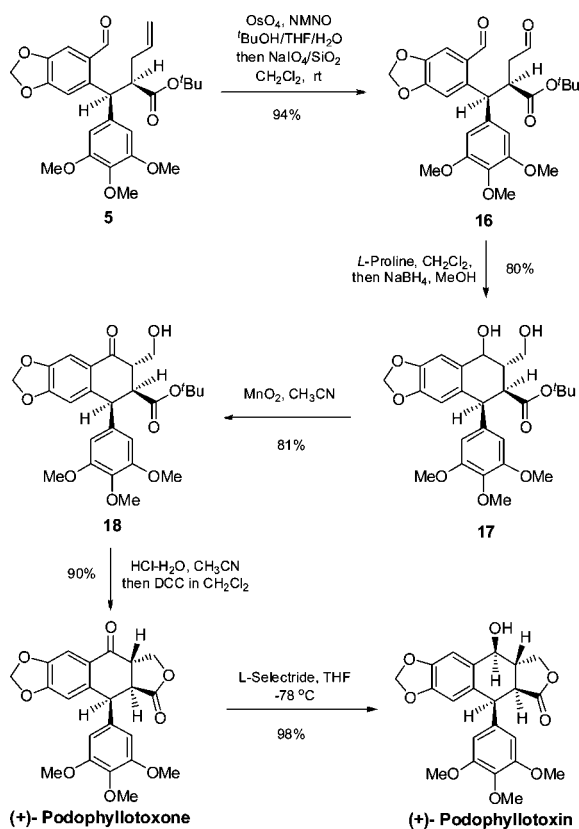


Figure 2. Results of asymmetric sequential conjugate addition–alkylation. Yields represent isolated yield based on cinnamic acid derivatives. The absolute configurations (as depicted) were established by comparison of optical rotation of the synthetic podophyllotoxin with that of natural podophyllotoxin. Diastereoselectivities (dr) were determined by ^1H NMR and enantioselectivities (ee) were determined by chiral HPLC on AD-H column. Racemic samples were prepared by utilization of 2-(1,3-dioxolan-2-yl)aryllithium. (a) Reaction was carried out at $-100\text{ }^\circ\text{C}$.

ent-podophyllotoxin in 98% yield as a single isomer and thus finalized the enantioselective synthesis ($[\alpha]_{\text{D}}^{27} = +91.8$, c 0.708, CHCl_3 , 99% ee by HPLC on an AD-H column).

In summary, we have developed an enantioselective strategy toward the total synthesis of (+)-podophyllotoxin. Starting from commercially available 3,4,5-trimethoxycinnamic acid, this new route leads to (+)-podophyllotoxin **1** in only eight steps with 29% overall yield. In comparison with previous synthetic routes,^{3,10} our new approach represents one of the most flexible, efficient, and concise routes. Although pseudoephedrine has been used as an

Scheme 4. Enantioselective Total Synthesis of (+)-Podophyllotoxin



auxiliary in asymmetric synthesis for many years, to the best of our knowledge, utilization of pseudoephedrine oxazolidine in an aryllithium Michael donor as demonstrated in this paper

has never been reported. The enantioselective version of the sequential addition-allylation should be of synthetic value for the synthesis of pharmaceuticals as well as natural products. This strategy, coupled with our previous synthetic route, lays a solid foundation for the synthesis of representative podophyllotoxin family as well as analogues that are of interests for medicinal chemistry.

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Supporting Information Available: ^1H and ^{13}C NMR and HPLC spectra of all key intermediates and experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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