Tetrahedron 68 (2012) 423–428

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Palladium(II)-catalyzed enyne cyclization strategies toward the podophyllotoxin ring system

Jason N. Abrams [a,*], Qi Zhao [b], Ion Ghiviriga [c], Minaruzzaman [a]

[a] Department of Chemistry, Xavier University of Louisiana, 1 Drexel Drive; New Orleans, LA 70125, USA
[b] Department of Chemistry, Tulane University, New Orleans, LA 70118, USA
[c] Department of Chemistry, University of Florida, Gainesville, FL 32611, USA

ARTICLE INFO

Article history:
Received 5 September 2011
Received in revised form 2 November 2011
Accepted 2 November 2011
Available online 10 November 2011

Dedicated to Professor Lu Xiyan on the occasion of his pioneering work on Pd(II)-catalyzed enyne cyclizations

Keywords:
Palladium-catalyzed
Enyne cyclization
Carboesterification
Podophyllotoxin
Etoposide
Anticancer

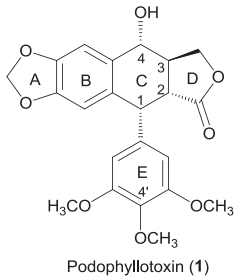
ABSTRACT

A functionally enriched ABCD ring system of podophyllotoxin was generated through Pd(II)-templated cyclization of an alkynoic alkene, prepared in five steps from commercially available 6-bromopiperonal. This research expands upon the recent carboesterification methodology of Dong et al. (*Angew. Chem., Int. Ed.* **2009**, *48*, 9690–9692) by the application of $PdCl_2(MeCN)_2$, LiCl, and $CuCl_2$ conditions, which yielded the desired podophyllotoxin scaffold with an embedded vinyl chloride moiety. Likewise, these conditions were successfully applied to a propargylic alkene prepared in three steps from 6-bromopiperonal. The resulting product contains the ABCD ring system of podophyllotoxin, but substitutes a D-ring furan for the D-ring lactone. Application of the recent methodology of Lu et al. (*J. Org. Chem.* **1995**, *60*, 1160–1169) on a related 1,6-enyne substrate led to functionalized α-methylene γ-butyrolactones instead ($Pd_2(dba)_3 \cdot CHCl_3$, LiBr, and $CuBr_2$). The latter conditions applied to an alkynoic alkene afforded the ABCD ring system of podophyllotoxin with a vinyl bromide group. These vinyl halides allow for derivatization at a critical juncture in order to access novel podophyllotoxin analogs.

1. Introduction

The aryltetralin lactone podophyllotoxin is a member of a group of lignans for which coniferyl alcohol is a key biosynthetic precursor via oxidative dimerization.[1] Podophyllotoxin is a major constituent of species of the genus *Podophyllum* (Berberidaceae). It is contained in the resin of the roots and rhizomes of two predominant species: Indian Podophyllum (*Podophyllum hexandrum* Royle) and the American Mayapple (*Podophyllum peltatum* L.).[2] In these plants, it is produced as a secondary metabolite and has been used as a component of traditional folk medicine in various cultures.[3] As illustrated in Fig. 1, podophyllotoxin[4] exhibits an intriguing architecture with four contiguous chiral centers, a rigid *trans*-lactone, and a pseudoaxial E-ring.

In addition to its unique and synthetically challenging structure, podophyllotoxin exhibits high antimitotic and apoptotic activity because of its high affinity for tubulin and mitotic spindles of dividing cells at metaphase.[5] It is this high toxicity that limits the utility of the molecule as an anticancer therapy agent. The toxicity manifests as nausea, diarrhea, vomiting, and injury to healthy tissues, including peripheral and autonomic neuropathy. Nevertheless, efforts to reduce these side effects led to the discovery of etoposide (VP-16) **2** as well as teniposide **3**, a related thiophene derivative. Etoposide is an epimeric glucopyranoside analog of podophyllotoxin in which 4′-*O*-demethyl-4-epipodophyllotoxin serves as the aglycone (Fig. 2).



Podophyllotoxin (**1**)

Fig. 1. Numbering and ring lettering systems of podophyllotoxin.

* Corresponding author. Tel.: +1 504 520 5075; fax: +1 504 520 7942; e-mail address: jabrams@xula.edu (J.N. Abrams).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.11.002

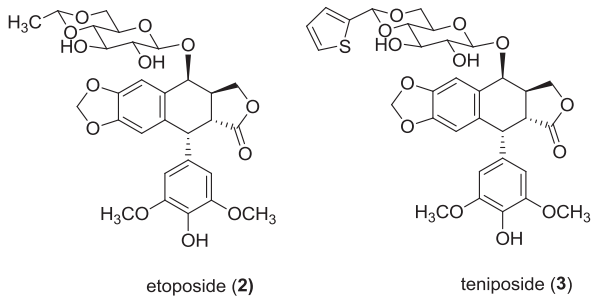


Fig. 2. Structure of etoposide (VP-16) and teniposide.

Etoposide's mechanism of action represents a good example of how a simple structural modification can dramatically affect biologically activity. Due to the bulky glucopyranoside moiety, etoposide does not bind to tubulin and does not act as a microtubule inhibitor, but instead forms a ternary complex with DNA and topoisomerase II.[6] The stability of this complex inhibits topoisomerase II from unwinding or untangling DNA, leading to DNA strand scission and, ultimately, apoptosis. Etoposide has been found clinically effective in the treatment of several cancers, including small-cell lung carcinoma, testicular cancer, and Kaposi's sarcoma.

The clinical promise of etoposide as an anticancer agent has, however, been subject to drug resistance,[7] possibly through alterations in apoptotic pathways or decreases in expression of topoisomerases,[8] poor oral bioavailability,[9] and myelosuppression (an especially high risk in cytotoxic chemotherapy for leukemia).[10] Therefore, developing clinically useful analogs of etoposide with improved selectivity requires a robust and versatile methodology for their synthesis.

Podophyllotoxin finds limited use as a synthetic precursor to potent analogs firstly because of its inherent chemical inflexibility to extensive structural modification. Secondly, the plant source with the highest podophyllotoxin content, *P. hexandrum* Royle, is overharvested and is considered an endangered species.[11]

Our group is interested in exploiting the unique reactivity of alkynes by incorporating recently developed methods into novel reaction sequences. Alkynes not only undergo a variety of functional group transformations but also often participate in tandem/cascade reaction processes in which several bonds are produced in a single operation. By exploiting the latter feature for step economy,[12] our group has focused on the pursuit of a synthetic strategy leading toward the ABCD ring scaffold of podophyllotoxin, which should allow for the preparation of novel analogs in a rapid and efficient manner.

2. Results and discussion

2.1. Initial synthetic route

α-Methylene γ-butyrolactones were selected as simple podophyllotoxin synthons from which to create novel analogs. Our initial retrosynthetic strategy toward this goal is outlined below (Scheme 1). Deoxypodophyllotoxin scaffold **4** is envisioned coming from methylene lactone ***Z*-5**, which can arise through a pivotal Pd(II)-catalyzed cyclization of allylic alkynoate **6**, itself readily accessible in three steps starting from 5-bromo-1,3-benzodioxole (**7**).

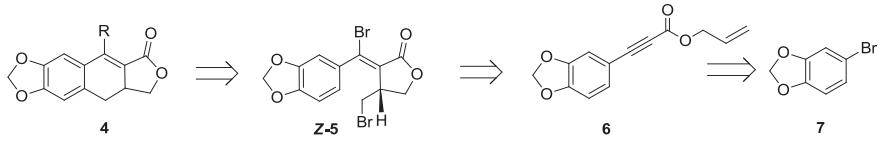
Preliminary work toward this target resulted from the single-step conversion of *p*-tolyl acetylene into lithium acetylide using *n*-butyllithium, followed by reaction with allyl chloroformate to give the corresponding enyne **9** (Scheme 2). The newly generated enyne alkynoate **9** was then treated under conditions developed by Lu et al.:[13] enyne **9** was exposed to tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3 \cdot CHCl_3$) in the presence of HOAc, $CuBr_2$, and LiBr to generate γ-lactone **10** with two bromine atoms that could be further elaborated in an orthogonal fashion. Unfortunately, the reaction produced two diastereomers in a roughly 1.5:1 *Z*/*E* ratio according to isolated yields and NMR analysis of the crude reaction mixture. This result contrasts with Lu's substituted enyne substrates, which underwent cyclization to provide almost exclusively the *Z*-exocyclic methylene diastereomer.

The configurations of the exocyclic methylenes of both ***Z*-10** and ***E*-10** diastereomers were determined using NOESY analysis.[14]

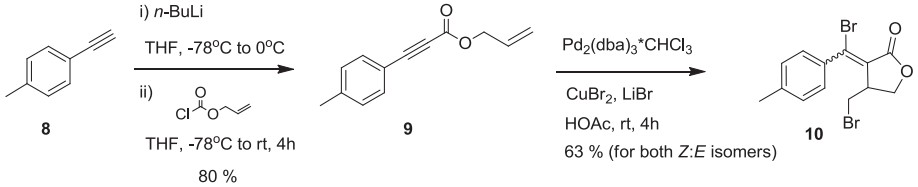
2.2. Synthesis of target system

5-Bromo-1,3-benzodioxole **7** was treated with TMS-acetylene under Sonogashira conditions to form aryl acetylene **11** (Scheme 3). The alkyne moiety of this intermediate was subsequently deprotected under standard conditions to form terminal alkyne **12**, which was then transformed into the desired enyne **6** through lithium acetylide formation, followed by coupling with allyl chloroformate. Upon exposure to in situ generated Pd(II)-templated cyclization conditions according to Lu's protocol, α-methylene γ-butyrolactones were formed cleanly and were isolated chromatographically in a 1.5:1 *Z*/*E* stereoisomeric ratio, as before in the simpler model system.[14]

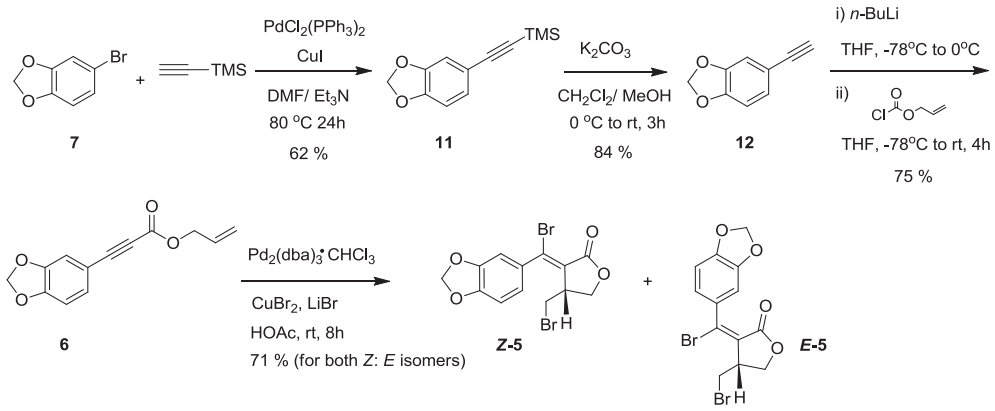
Z-configured methylene lactones (***Z*-5** and ***Z*-10**) contain two orthogonally reactive halides providing a concise route toward the target tetralin scaffold of podophyllotoxin. Accordingly, in an



Scheme 1. Retrosynthetic strategy toward ABCD rings of deoxypodophyllotoxin.

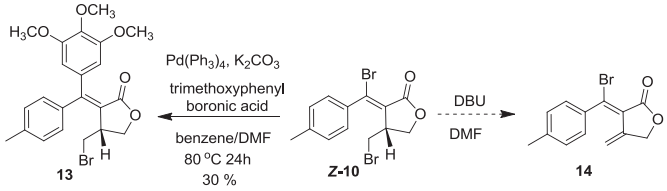


Scheme 2. Synthesis of model α-methylene γ-butyrolactone.



Scheme 3. Formation of target enyne system followed by Pd(II)-catalyzed cyclization.

initial elaboration study, the vinyl bromide of the more readily accessible ***Z*-10** was successfully reacted with trimethoxyphenyl boronic acid under typical Suzuki conditions to form diaryl methylene lactone **13**, albeit on an unoptimized small scale (Scheme 4), while 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-induced alkyl dehydrohalogenation appeared to provide *exo*-methylene product **14**, according to ^{1}H NMR analysis of the crude reaction mixture. Nevertheless, subsequent attempts at purification proved unfruitful.



Scheme 4. Elaboration of model α-methylene γ-butyrolactone ***Z*-10**.

We envisioned the possibility of convergence of our α-methylene γ-butyrolactone advanced substrate with end-game strategies that have recently been employed. However, as discussed, a technical hurdle surfaced: a lack of diastereocontrol during the transformation of our allylic alkynoate substrates. This was evidenced by the resulting product mixtures, with both *E* and *Z* double bond geometry on the exocyclic alkene.

2.3. Second-generation retrosynthetic strategy

Therefore, another strategy was required, one that utilized an alternative Pd(II)-catalyzed enyne cyclization involving intramolecular carboesterification of an alkynoic alkene[15] and occurring via a formal [3+2] cycloaddition pathway. With the ABCD ring scaffold in hand, the vinyl halide moiety might be transformed into a variety of E-rings under Suzuki[16] conditions with arylboronic acids serving as the coupling partner (Fig. 3).

Retrosynthetically, as shown in Scheme 5, functionally enriched scaffold **15** was envisioned coming from alkynoic alkene **16** via Pd(II)-catalyzed intramolecular carboesterification. In turn, substrate **16** could be arrived at expeditiously by protection of the allylic alcohol of substrate **17**, coupling of terminal alkyne with a chloroformate, and then saponification of the resulting alkynoate ester. And alkyne **17** could arise via vinyl Grignard addition to 6-bromopiperonal (**18**), followed by a Sonogashira reaction[17] between an aryl bromide and TMS-acetylene.

2.4. Synthesis of target system

According to the retrosynthetic path depicted, synthesis began with inexpensive, commercially available 6-bromopiperonal **18** (Scheme 6). Vinyl Grignard addition to **18** cleanly provided allylic alcohol **19** in high yield. Substrate **19** was next subjected to Sonogashira reaction conditions with TMS-acetylene to provide phenyl acetylene **20**, which was smoothly converted into terminal alkyne

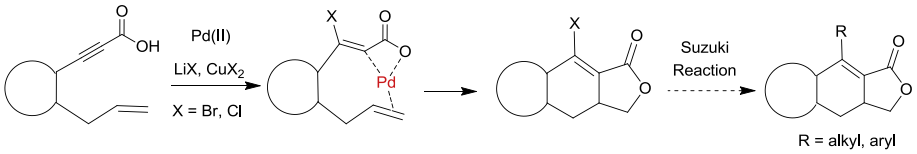
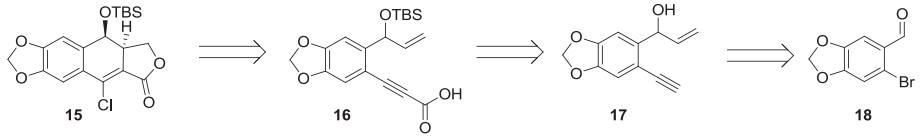
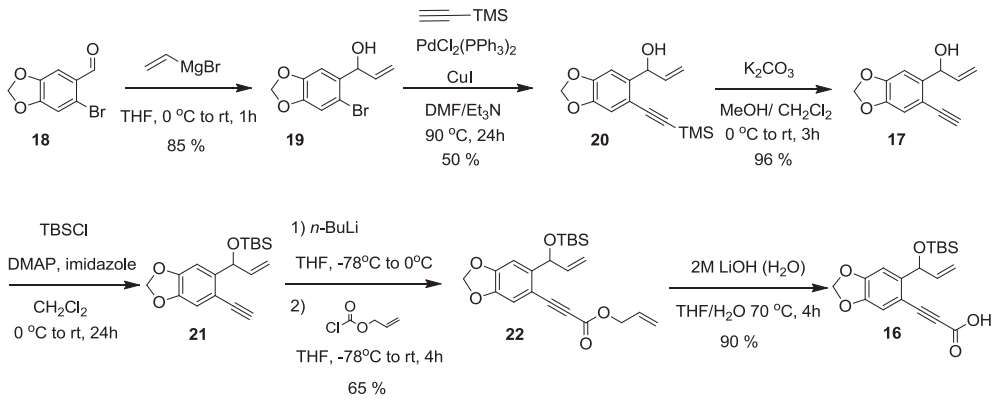


Fig. 3. Formal [3+2] cycloaddition of alkynoic alkene and subsequent elaboration.



Scheme 5. Alternative Pd(II)-catalyzed enyne cyclization retrosynthetic strategy.

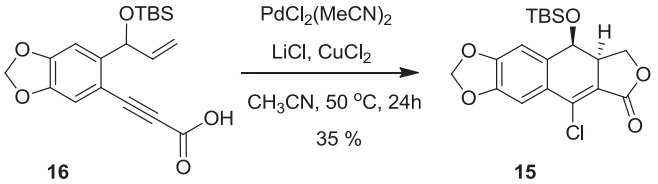


Scheme 6. Construction of cyclization precursor alkynoic alkene **16**.

17. The alcohol moiety of **17** was next protected with TBS chloride to furnish silyl ether **21**.[18] In this regard, substrate **21** was first converted into the requisite lithium acetylide before addition of allyl chloroformate to form alkynoate **22**.[19] Finally, alkynoate **22** was transformed into alkynoic alkene **16**, the Pd(II)-catalyzed cyclization precursor, under typical saponification conditions. Interestingly, the in situ generated lithium acetylide of terminal alkyne **21** can be exposed to dry ice, rather than a chloroformate source, to form substrate **16** directly, thereby eliminating one step.[20]

Synthesis of scaffold **15** from alkynoic acid **16** was carried out under conditions recently identified by Dong et al. regarding palladium-catalyzed intramolecular carboesterification of olefins.[15]

Accordingly, a stock solution of $PdCl_2(MeCN)_2$ in acetonitrile was added to alkynoic acid **16**, LiCl, and $CuCl_2$ in acetonitrile (Scheme 7). Complete consumption of the starting material was effected by stirring at 50 °C for 24–48 h to afford **15**. The proposed mechanism for this palladium-catalyzed intramolecular carboesterification is virtually analogous to that reported originally by Lu et al. for allylic alkynoates.[13]



Scheme 7. Cyclization of alkynoic alkene **16** to tetralin scaffold **15**.

We only discerned and isolated a single diastereomer, with a *cis*-relative configuration of hydrogens on C3–C4 of the ring junction D/C and ring-C, respectively. The structure of **15** was definitively established by NMR studies.[21]

In the 1D selective nuclear Overhauser effect (NOE) spectra, with selective irradiation at δ 3.51 ppm (H_C), a very strong doublet at δ 4.56 ppm (H_D) was observed (Fig. 4). This strong NOE effect between H_D and H_C shows that both protons are close in space,

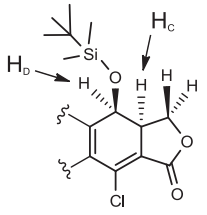
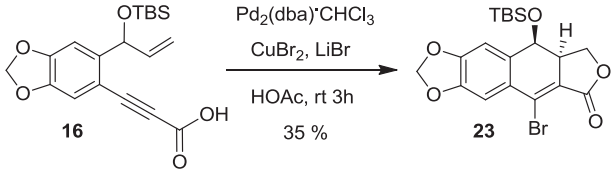


Fig. 4. Conformational analysis of product **15**.

which supports a cis configuration. In addition, a smaller coupling constant (J=3.8 Hz) between H_D and H_C in the ^{1}H NMR spectrum is also consistent with this finding.

2.5. Synthesis of target system part II

We were also interested in subjecting alkynoic alkene **16** to the Pd(II)-catalyzed cyclization conditions originally used for the preparation of our α-methylene γ-butyrolactones. To this end, alkynoic alkene **16** was treated with 5 mol % $Pd_2(dba)_3\cdot CHCl_3$, along with 6 equiv of lithium bromide and 3 equiv of copper(II) bromide, while stirring at room temperature in glacial acetic acid (Scheme 8). The reaction was monitored by TLC for disappearance of the starting material. Cyclized product **23** has the same relative stereochemistry in comparison to cyclized product **15**.



Scheme 8. Cyclization of alkynoic alkene **16** to tetralin scaffold **23**.

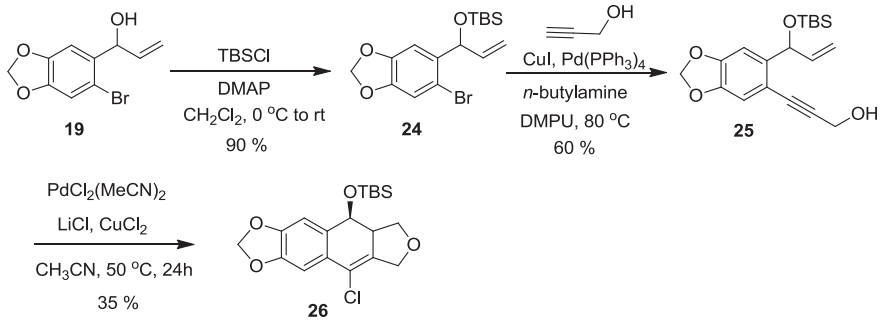
2.6. Synthesis of simpler system

Podophyllotoxin-related compounds containing a *trans*-fused delactonized ring-D were prepared by Gensler et al.[22] The non-enolizable nature of these analogs allowed them to have enhanced physiological lifetimes as a consequence of minimized metabolic C-2 epimerization. Most retained activity as tubulin polymerization inhibitors, although with less pronounced cytotoxicity.

With this in mind, and to further explore the opportunity of preparing podophyllotoxin scaffolds in a step-economical fashion,[12] we investigated the cyclization of propargylic species **25**, which is readily accessible in only three steps starting from 6-bromopiperonal (Scheme 9).

The previously described method for the preparation of allyl alcohol **19** was followed by protection of the resulting free alcohol with TBS chloride to form silyl ether **24**. This species was then subjected to Sonogashira reaction conditions with propargyl alcohol to form the desired cyclization precursor **25**. Sonogashira cross-coupling occurred in modest yield via a recently described procedure.[23]

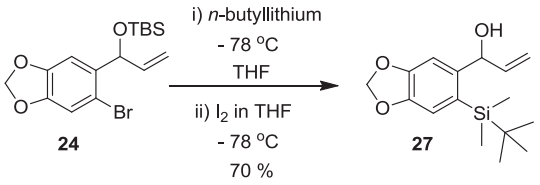
These atypical conditions employed $Pd_2(dba)_3\cdot CHCl_3$, copper iodide, *n*-butylamine, and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-



Scheme 9. Cyclization of propargyl alcohol substrate **25** to tetralin scaffold **26**.

pyrimidinone (DMPU) as the reaction solvent. The reaction mixture was heated at 80 °C in a sealed tube for 24 h to provide substrate **25** in moderate yield. Subsequent conversion of **25** into product **26** employed the same conditions as the cyclization of carboxylic acid substrate **16**. The relative configuration of product **26** was assigned by comparison of its NMR spectra with that of products **15** and **23**.

As an aside, our initial efforts to utilize traditional Sonogashira reaction conditions ($PdCl_2(PPh_3)_2$, triethylamine, copper iodide, and DMF) (Scheme 9) between substrate **24** and propargyl alcohol led to poor yield. We therefore attempted conversion of **24** into an iodinated species, envisioning its enhanced cross-coupling ability. In this manner, lithium–halogen exchange was promoted with the addition of *n*-butyllithium followed by the addition of iodine. However, the intended iodinated product was not produced, as most of the reaction formed silane species **27**, via a retro-Brook rearrangement (Scheme 10).[24] This result led us to investigate our currently employed Sonogashira conditions.[23]



Scheme 10. Formation of retro-Brook rearrangement product.

3. Conclusions

This paper reports the preparation of α-methylene γ-butyrolactones from alkenyl propynoates. The inability to transform these products into the desired ABCD ring scaffold of podophyllotoxin led our group to focus on cyclization studies of alkynoic alkene substrate **16**. To this end, we employed two similar catalytic systems, which yielded tetralin products **15** and **23**. Cyclization studies on a simpler substrate **25** also led to tetralin product **26**. Therefore, this study demonstrates the feasibility of exploiting the properly embedded vinyl halide functionality to elaborate substrates **15** or **23** or **26** toward podophyllotoxin and etoposide derivatization via cross-coupling protocols.

Our racemic approach toward the podophyllotoxin ABCD ring system is unique in several respects.[25] Some previous syntheses utilize more labile intermediates[26] or a large number of steps,[27] thus thwarting the economical feasibility of large-scale production. The E-ring is considered a crucial moiety for podophyllotoxin's biological activity. Contemporary strategies introduce the pendent E-ring at an early stage,[28] hampering the ability to prepare analogs at this position. By contrast, this study developed a modular synthetic route that allows for the introduction of E-ring variation at a late stage. This should facilitate the continual discovery of biologically active podophyllotoxin derivatives.[29]

Future work will entail tuning the reaction conditions to improve the yield of desired scaffolds.[30] Such optimization will enhance this strategy's potential for use in the development of therapeutic leads through function-oriented synthesis (FOS)[12] in an atom-economic fashion.[31] This could be particularly applicable to the simpler sequence leading to substrate **26**. In addition to improving the yield of desired products, future work will also explore other relevant transformations of ABCD ring scaffolds.[32]

Acknowledgements

We gratefully acknowledge the Louisiana Cancer Research Consortium (LCRC), the Research Centers for Minority Institutes (RCMI) (NIH 1G12RR026260), and Center for Undergraduate Research (CUR) for funding for this project. We are especially thankful for the time afforded on the 500-MHz Bruker NMR spectrometer at Tulane University's Coordinated Instrument Facility as well as the NMR instrument facility at the University of New Orleans. We thank the University of Florida Mass Spec Services, and in particular, Dr. David H. Powell, Dr. Maria C. Dancel, Dr. Jodie Johnson, and Noelle Elliott for all the mass spectral data. We are also thankful to Dr. Neil R. McIntyre of Xavier University for his editing suggestions. Finally, we acknowledge the RCMI core at Xavier University.

Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.11.002.

References and notes

1. (a) Yousefzadi, M.; Sharifi, M.; Behmanesh, M.; Moyano, E.; Bonfill, M.; Cusido, R. M.; Palazon, J. *Eng. Life Sci.* **2010**, *10*, 281–292; (b) Canel, C.; Moraes, R. M.; Dayan, F. E.; Ferreira, D. *Phytochemistry* **2000**, *54*, 115–120.
2. (a) Ayres, D. C.; Loike, J. D. In *Lignans: Chemical, Biological and Clinical Properties (Chemistry and Pharmacology of Natural Products)*; Phillipson, J. D., Ayres, D. C., Baxter, H., Eds.; Cambridge University: Cambridge, UK, 1990; (b) Gordaliza, M.; García, P. A.; Miguel del Corral, J. M.; Castro, M. A.; Gómez-Zurita, M. A. *Toxicon* **2004**, *44*, 441–459.
3. Fukuda, Y.; Osawa, T.; Namiki, M.; Ozaki, T. *Agric. Biol. Chem.* **1985**, *49*, 301–306.
4. Liu, Y. Q.; Yang, L.; Tian, X. *Curr. Bioact. Compd.* **2007**, *3*, 37–66.
5. (a) Loike, J. D.; Horwitz, S. B. *Biochemistry* **1976**, *15*, 5435–5443; (b) Loike, J. D.; Brewer, C. F.; Sternlicht, H.; Gensler, W. J.; Horwitz, S. B. *Cancer Res.* **1978**, *38*, 2688–2693.
6. (a) Meresse, P.; Dechaux, E.; Monneret, C.; Bertounesque, E. *Curr. Med. Chem.* **2004**, *11*, 2443–2466; (b) Issell, B. F.; Tihon, C.; Curry, M. E. *Cancer Chemother. Pharmacol.* **1982**, *7*, 113–115; (c) Minocha, A.; Long, B. H. *Biochem. Biophys. Res. Commun.* **1984**, *122*, 165–170.
7. Helmbach, H.; Kern, M. A.; Rossmann, E.; Renz, K.; Kissel, C.; Gschwendt, B.; Schadendorf, D. *J. Invest. Dermatol.* **2002**, *118*, 923–932.
8. Asano, T.; An, T.; Mayes, J.; Zwelling, L. A.; Kleinerman, E. S. *Biochem. J.* **1996**, *319*, 307–317.
9. Etoposide phosphate was designed by Bristol–Myers Squibb as a pro-drug with greater water solubility than etoposide, it can be administered intravenously at

higher doses and is rapidly converted by phosphatases in the plasma to etoposide. For another analog with twice the water solubility of etoposide, see Yoshida, M.; Kobunai, T.; Aoyagi, K.; Saito, H.; Utsugi, T.; Wierzba, K.; Yamada, Y. *Clin. Cancer Res.* **2000**, *6*, 4396–4401.
10. Kobayashi, K.; Ratain, M. J. *Cancer Chemother. Pharmacol.* **1994**, *34*, S64–S68.
11. Alam, M. A.; Gulati, P.; Gulati, A. K.; Mishra, G. P.; Naik, P. K. *Indian J. Biotechnol.* **2009**, *8*, 391–399.
12. Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40–49.
13. Ji, J.; Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1160–1169.
14. NOESY and gHMBC NMR analyses were performed on all α-methylene γ-butyrolactones. See Supplementary data, Chemical Shift Assignments, Compounds ***E*-5**, ***E*-10**, ***Z*-5**, ***Z*-10**, pp 12–13.
15. Li, Y.; Jardine, K. J.; Tan, R.; Song, D.; Dong, V. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9690–9692.
16. (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437–3440; (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. For recent studies, see: (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028; (d) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
17. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
18. Initially, substrate **17** was treated with 2.1 equiv of *n*-butyllithium, followed by 1 equiv of allyl chloroformate, yet produced exclusively the undesired carbonate.
19. Ethyl chloroformate was also employed to form the corresponding ethyl enyne alkynoate. However, the subsequent saponification appeared to proceed more smoothly with the analogous allyl enyne alkynoate.
20. Ganolix Lifescience recently prepared substrate **16** for our group using this route. These materials are allocated for future analog development with the Louisiana Cancer Research Consortium (LCRC) Molecular Biology Core. See Supplementary data, p 4.
21. These structural elucidations were performed through a combination of HMBC and NOESY NMR techniques. See Supplementary data, Chemical Shift Assignments Compounds **15**, pp 11–12.
22. Walter, J.; Gensler, W. J.; Murthy, C. D.; Trammell, M. H. *J. Med. Chem.* **1977**, *20*, 635–644.
23. Houpis, I. N.; Shilds, D.; Nettekoven, U.; Schnyder, A.; Bappert, E.; Weerts, K.; Canters, M.; Vermuelen, W. *Org. Process Res. Dev.* **2009**, *13*, 598–606.
24. For spectral data of the silane compound, see Supporting Information, p 10. For an original reference, see: (a) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77–84; (b) For a review relating to [1,4] and [1,5] Brook and retro-Brook rearrangements, see Lautens, M.; Delanghe, P. H. M.; Goh, J. B.; Zhang, C. H. *J. Org. Chem.* **1995**, *60*, 4213–4227.
25. Below are representative examples of entry to podophyllotoxin and related compounds. For routes involving intramolecular cycloaddition/Diels–Alder reactions of substituted *o*-quinodimethanes, see: (a) Jung, M. E.; Yuk-Sun Lam, P.; Mansuri, M. M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087–1105; (b) Macdonald, D. I.; Durst, T. *J. Org. Chem.* **1986**, *51*, 4749–4750; (c) Kraus, G. A.; Wu, Y. *J. Org. Chem.* **1992**, *57*, 2922–2925. For other Diels–Alder approaches, see: (d) Bush, E. J.; Jones, D. W. C. S. *J. Chem. Soc., Chem. Commun.* **1993**, 1200–1201. For tandem-conjugate addition routes, see: (e) Wu, Y.; Zhao, J.; Chen, J.; Pan, C.; Li, L.; Zhang, H. *Org. Lett.* **2009**, *11*, 597–600; (f) Hadimani, S. B.; Tanpure, R. P.; Bhat, S. V. *Tetrahedron Lett.* **1996**, *37*, 4791–4794; (g) Harrowven, D. C. *Tetrahedron* **1993**, *49*, 9039–9048; (h) Stadler, D.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7557–7559; (i) For a palladium-catalyzed approach, see Charruault, L.; Michelet, V.; Genêt, J.-P. *Tetrahedron Lett.* **2002**, *43*, 4757–4760; (j) For an aryl radical cyclization approach, see Ishibashi, H.; Ito, K.; Hirano, T.; Tabuchi, M.; Ikeda, M. *Tetrahedron* **1993**, *49*, 4173–4182.
26. For example, see Ref. 25b.
27. Many syntheses employ at least 13 steps or more from commercially available starting materials: see citations in Ref. 25. For a review of synthetic approaches to the Podophyllum lignans, see: (a) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75–96; (b) Ward, R. S. *Phytochem. Rev.* **2003**, *2*, 391–400.
28. The majority of studies cited in Ref. 25. install the E-ring at an early stage.
29. For brief reviews of E-ring modifications to podophyllotoxin, see: (a) Ref. 2b. For studies validating the functional importance of the E-ring of etoposide, see: (b) Wilstermann, A. M.; Bender, R. P.; Godfrey, M.; Choi, S.; Anklin, C.; Berkowitz, D. B.; Osheroff, N.; Graves, D. E. *Biochemistry* **2007**, *46*, 8217–8225.
30. The major byproduct from transformation of **16** into **15** has been isolated. Extensive spectral analysis has lead to its tentative assignment as a tetralone cyclopropane. See Supplementary data, pp 15–16.
31. Trost, B. M. *Science* **1991**, *254*, 1471–1477.
32. For example, spectral evidence for the conversion of the D-ring lactone moiety of substrate **15** into a lactam derivative has been found. See Supplementary data, p 16.