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A Novel, Expeditious Synthesis of Racemic Camptothecin

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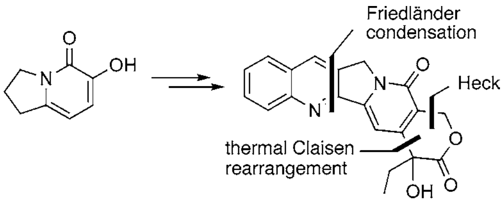
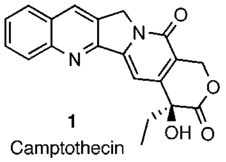
ABSTRACT



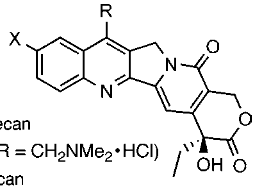
Camptothecin

A novel and efficient synthesis of racemic camptothecin, starting from a readily accessible hydroxy pyridone, is presented. Key steps include a Claisen rearrangement of a functionalized allylic ether, a hindered Heck coupling, and a Friedländer condensation.

Isolated from the Chinese plant *Camptotheca acuminata* by Wall and co-workers in 1966, camptothecin (**1**) elicited widespread interest due to its potent antitumor activity.[1,2] The initial excitement quickly waned, however, because of problems associated with its insolubility and toxicity. Several years later,[3] though, it was reported that camptothecin had a unique mechanism of action that involved selective inhibition of DNA topoisomerase I. This disclosure served to rekindle interest in camptothecinoids and has led to topotecan (**2a**)[4] and irinotecan (**2b**),[5] as well as several other analogues[6] currently in clinical and preclinical trials.



1
Camptothecin



2a, Topotecan
(X = OH, R = $CH_2NMe_2 \cdot HCl$)
b, Irinotecan
(X = OCOPipPip, R = Et)

The camptothecinoids and camptothecin in particular have been targeted by numerous research groups, which has resulted in many imaginative syntheses over the past several decades.[2] Although several of the approaches are direct and high-yielding, for the most part they are not open to facile variation. We have previously described a route to the camptothecinoids based on a bicyclization strategy.[7] In this communication we wish to disclose a conceptually different approach founded on a 1,3-dipolar cycloaddition.[8] This new camptothecinoid approach, now demonstrated by the prepa-

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[1] Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; MacPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888−3890.

[2] For reviews on camptothecin and its derivatives, see: (a) Du, W. *Tetrahedron* **2003**, *59*, 8649−8687. (b) Lansiaux, A.; Bailly, C. *Bull. Cancer* **2003**, *90*, 239−245. (c) *Camptothecins: New Anticancer Agents*; Potmesil, M., Pinedo, H., Eds.; CRC Press: Boca Raton, 1995. (d) Sawada, S.; Yokokura, T.; Miyasaka, T. *Curr. Pharm. Des.* **1995**, *1*, 113−132. (e) Torck, M.; Pinkas, M. *J. Pharm. Belg.* **1996**, *51*, 200−207. (f) Hutchinson, C. R. *Tetrahedron* **1981**, *37*, 1047−1065.

[3] Hsiang, Y. H.; Hertzberg, R.; Hecht, S.; Liu, L. F. *J. Biol. Chem.* **1985**, *260*, 14873−14878. See also: Rothenberg, M. L. *Ann. Oncol.* **1997**, *8*, 837−855. Pommier, Y.; Pourquier, P.; Fan, Y.; Strumberg, D. *Biochim. Biophys. Acta* **1998**, *1400*, 83−105. Palumbo, M.; Gatto, B.; Sissi, C. In *DNA and RNA Binders*; Demeunynck, M., Bailly, C., Wilson, W. D., Eds.; Wiley: Weinheim, 2003; Vol. 2, Chapter 19.

[4] Kingsbury, W. D.; Boehm, J. C.; Jakas, D. R.; Holden, K. G.; Hecht, S. M.; Gallagher, G.; Caranfa, M. J.; McCabe, F. L.; Faucette, L. F.; Johnson, R. K.; Hertzberg, R. P. *J. Med. Chem.* **1991**, *34*, 98−107.

[5] Negoro, S.; Fukuoka, M.; Masuda, N.; Takada, M.; Kusunoki, Y.; Matsui, K.; Takifuji, N.; Kudoh, S.; Niitani, H.; Taguchi, T. *J. Natl. Cancer Inst.* **1991**, *83*, 1164−1168. Kawato, Y.; Aonuma, M.; Hirota, Y.; Kuga, H.; Sato, K. *Cancer Res.* **1991**, *51*, 4187−4191.

[6] Cragg, G. M.; Newman, D. J. *J. Nat. Prod.* **2004**, *67*, 232−244. Butler, M. S. *Nat. Prod. Rep.* **2005**, *22*, 162−195.

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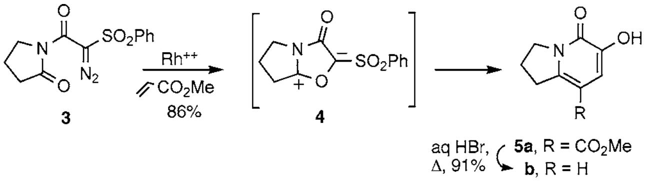
ration of camptothecin (as its racemate), is convergent at several points, which should make it well-suited for eventual structural modification of the natural product.

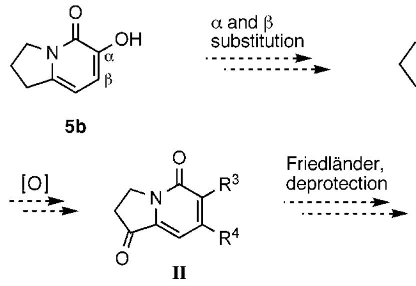
Padwa and co-workers have developed over the past several years elegant chemistry based on isomünchnone cycloadditions.[9,10] In a particularly interesting example,[9a] diazo imide **3** was converted into isomünchnone **4**, which underwent cycloaddition in situ with methyl acrylate to furnish, ultimately, hydroxy pyridone **5a**; treatment of **5a** with acid readily yielded hydroxy pyridone **5b** (Scheme 1).

Scheme 1



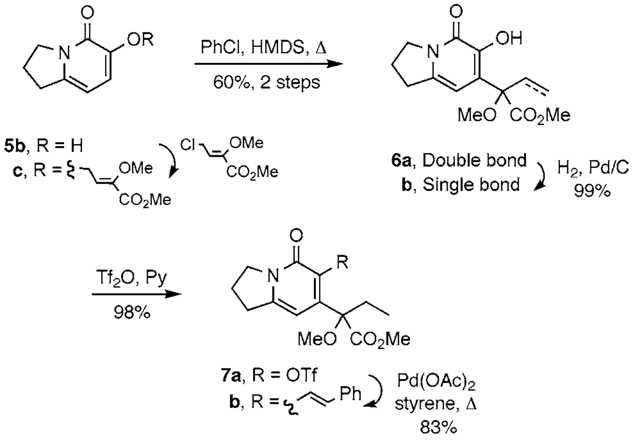
We felt that this hydroxy pyridone might serve as a precursor of a wide range of camptothecinoids if (1) appropriate appendages for eventual hydroxy lactone construction could be joined to **5b** at the α and *β* positions to give **I**; (2) benzylic-type oxidation could be achieved at some point in the presence of existing functionality to produce **II**; (3) Friedländer condensation and eventual hydroxyl-group deprotection could be accomplished (Scheme 2).

Scheme 2



The synthesis began with etherification of hydroxy pyridone **5b** with (*Z*)-methyl 4-chloro-2-methoxybut-2-enoate[11] and cesium carbonate to give derivative **5c**, in preparation for a Claisen rearrangement to introduce a substituent in the *β* position (Scheme 3). This etherification proved uneventful, as did the subsequent thermally induced Claisen rearrangement,[12] and hydroxy pyridone **6a** could be secured in good yield. Hydrogenation of **6a** over Pd/C then afforded hydroxy pyridone **6b**, in which the desired *β* substituent was now in place.

Scheme 3



The introduction of the α substituent proved to be much more problematic. The derived triflate **7a** failed to yield serviceable amounts of α coupled product with a large array of palladium catalysts, ligands, and tin and boron reagents. Several standard Heck procedures with styrene or methyl acrylate were also examined for this transformation but afforded the desired product in, at best, moderate yield. Fortunately, however, greater success was achieved under Jeffery's conditions:[13] palladium acetate in conjunction with tetrabutylammonium acetate in acetonitrile at 80 °C delivered the styryl derivative **7b** in a remarkable 83% yield.

Lactone construction was completed by treatment of **7b** with ozone in the presence of pyridine at −100 °C, followed by reduction of the resultant aldehyde with sodium borohydride, which provided lactone **8** in 80% overall yield (Scheme 4). Of the protocols examined for benzylic-type oxidation of lactone **8** or other intermediates (e.g., α-formyl and α-styryl derivatives), selenium dioxide[14] with **8** proved to

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(7) Mekouar, K.; Génisson, Y.; Leue, S.; Greene, A. E. FR 99 06757, May, 1999. Leue, S.; Garçon, S.; Greene, A. E.; Génisson, Y.; Léon, P. FR 00 11769, September, 2000. Leue, S.; Miao, W.; Kanazawa, A.; Génisson, Y.; Garçon, S.; Greene, A. E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2903−2905.

(8) The present work represents a significant extension of our earlier mappicine ketone (nothapodytine B) synthesis. See: Raolji, G. B.; Garçon, S.; Greene, A. E.; Kanazawa, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 5059−5061.

(9) (a) Padwa, A.; Sheehan, S. M.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 8648−8659. See, also: (b) Hertzog, D. L.; Austin, D. J.; Nadler, W. R.; Padwa, A. *Tetrahedron Lett.* **1992**, *33*, 4731−4734. (c) Padwa, A.; Hertzog, D. L.; Nadler, W. R.; Osterhout, M. H.; Price, A. T. *J. Org. Chem.* **1994**, *59*, 1418−1427. (d) Marino, J. P., Jr.; Osterhout, M. H.; Price, A. T.; Semones, M. A.; Padwa, A. *J. Org. Chem.* **1994**, *59*, 5518−5520. (e) Padwa, A.; Hertzog, D. L.; Nadler, W. R. *J. Org. Chem.* **1994**, *59*, 7072−7084. (f) Marino, J. P., Jr.; Osterhout, M. H.; Padwa, A. *J. Org. Chem.* **1995**, *60*, 2704−2713. (g) Sheehan, S. M.; Padwa, A. *J. Org. Chem.* **1997**, *62*, 438−439. (h) Harris, J. M.; Padwa, A. *Org. Lett.* **2003**, *5*, 4195−4197.

(10) For reviews on isomünchnone cycloadditions, see: McMills, M. C.; Wright, D. In *The Chemistry of Heterocyclic Compounds: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley and Sons: New York, 2002; pp 253−314. Mehta, G.; Muthusamy, S. *Tetrahedron* **2002**, *58*, 9477−9504. Padwa, A. *Top. Curr. Chem.* **1997**, *189*, 121−158. Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223−269. Osterhout, M. H.; Nadler, W. R.; Padwa, A. *Synthesis*, **1994**, 123−141. Padwa, A. *Acc. Chem. Res.* **1991**, *24*, 22−28.

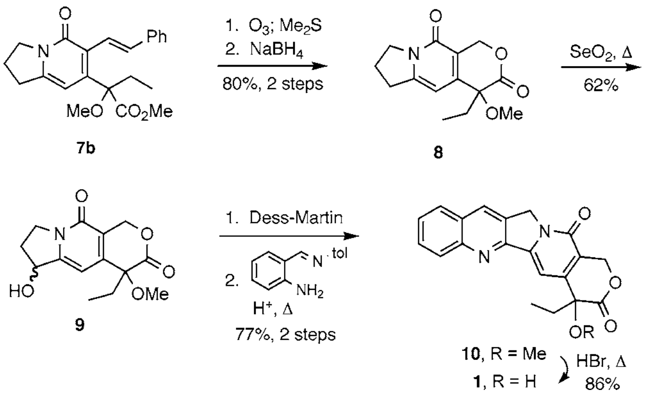
(11) Farina, C.; Gagliardi, S.; Parini, C.; Pinza, M.; Nadler, G.; Marguerite, M. G.; Morvan, M. J-M. PCT Int. Appl. WO 9621644, 1996.

(12) For reviews on the Claisen rearrangement, see: Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1−252. Blechert, S. *Synthesis* **1989**, 71−82. Martin Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939−3002.

(13) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113−10130. For Pd couplings on related substrates, see: Earl, R. A.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 4786−4800 and ref 9a.

(14) Shen, W.; Coburn, C. A.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 611−617.

Scheme 4



be the most efficacious and afforded the hydroxy derivative **9** in 62% yield (68% brsm).[15] As the corresponding crude ketone, formed with the Dess−Martin periodinane, proved unstable to purification, it was directly subjected to Friedländer condensation[14,16] with an *o*-aminobenzaldehyde surrogate to afford quinoline **10** in 77% yield (2 steps). Since we had previously found camptothecin to be surprisingly stable in hot aqueous HBr, these conditions were applied to cleave the methyl protecting group in **10**, which indeed smoothly provided camptothecin in 86% yield. The synthetic material (mp 264−265 °C, dec) was chromatographically and spectroscopically identical with an authentic sample of the natural product.

To summarize, a new approach to camptothecin and its congeners, which is both concise and efficient, has been developed from readily available hydroxy pyridone **5b**. The approach offers excellent opportunities for asymmetric induction;[17] these modifications, as well as other aspects, are presently being studied and will be discussed in a future publication.

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Supporting Information Available: Complete experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] Selenium dioxide oxidation of styryl derivative **7b** proceeded more rapidly, but the hydroxy product was less stable to SiO_2 purification, which resulted in a lower isolated yield.

[16] For a review on the Friedländer quinoline synthesis, see: Cheng, C.-C.; Yan, S. J. *Org. React.* **1982**, *28*, 37−201.

[17] See: Nubbemeyer, U. *Synthesis* **2003**, 961−1008. Abraham, L.; Körner, M.; Hiersemann, M. *Tetrahedron Lett.* **2004**, *45*, 3647−3650 and references therein.