ORGANIC LETTERS

2006
Vol. 8, No. 20
4665−4667

Synthesis of the Parent and Substituted Tetracyclic ABCD Ring Cores of Camptothecins via 1-(3-Aryl-2-propynyl)-1,6-dihydro-6-oxo-2-pyridinecarbonitriles

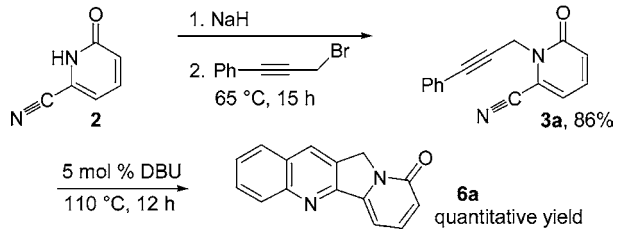
Weixiang Dai, Jeffrey L. Petersen,† and Kung K. Wang*

C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506-6045

kung.wang@mail.wvu.edu

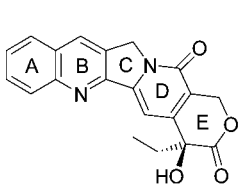
Received August 16, 2006

ABSTRACT

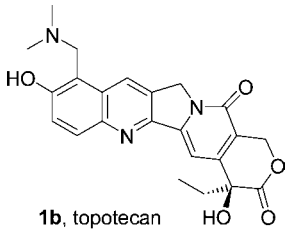


A new synthetic pathway to the parent and substituted ABCD ring cores of the camptothecin family of alkaloids was developed. The *N*-alkylation of 1,6-dihydro-6-oxo-2-pyridinecarbonitrile (2) with 3-bromo-1-phenylpropyne provided 3a using Curran's protocol. Treatment of 3a with a catalytic amount of DBU (5 mol %) at 110 °C for 12 h produced indolizino[1,2-*b*]quinolin-9(11*H*)-one (6a), the parent ABCD ring core of camptothecin, in essentially quantitative yield.

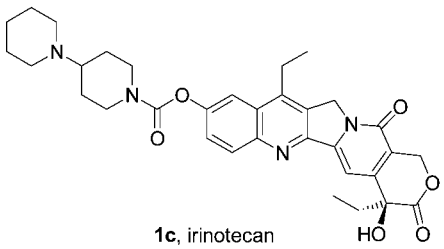
The potent antitumor activities of the camptothecin family of alkaloids have stimulated intense interest in developing synthetic methods for the parent (20*S*)-camptothecin (**1a**) and related analogues.[1] Diverse approaches to the assembly of the pentacyclic ring structure have been reported.[1b] The efforts have borne fruits with the approval of topotecan (**1b**) by the FDA for the treatment of ovarian cancer and small-cell lung cancer[2] and irinotecan (**1c**) for refractory colorectal cancer.[3] Several other camptothecin analogues are also in various stages of clinical trials.



1a, (20*S*)-camptothecin



1b, topotecan



1c, irinotecan

While the lactone E ring of camptothecins is essential in targeting DNA topoisomerase I,[4] the ABCD ring core can be modified with substituents to promote DNA binding.[5] We recently reported the use of a benzannulated enallene−isonitrile for the construction of a dimethylamino-substituted AB-

† To whom correspondence concerning the X-ray structures should be addressed. Phone: (304) 293-3435, ext 6423. Fax: (304) 293-4904. E-mail: jeffrey.petersen@mail.wvu.edu.

(1) For recent reviews, see: (a) Wall, M. E.; Wani, M. C. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 50, pp 509−536. (b) Du, W. *Tetrahedron* **2003**, *59*, 8649−8687.

(2) (a) Ormrod, D.; Spencer, C. M. *Drugs* **1999**, *58*, 533−551. (b) Herzog, T. J. *Oncologist* **2002**, *7* (Suppl. 5), 3−10.

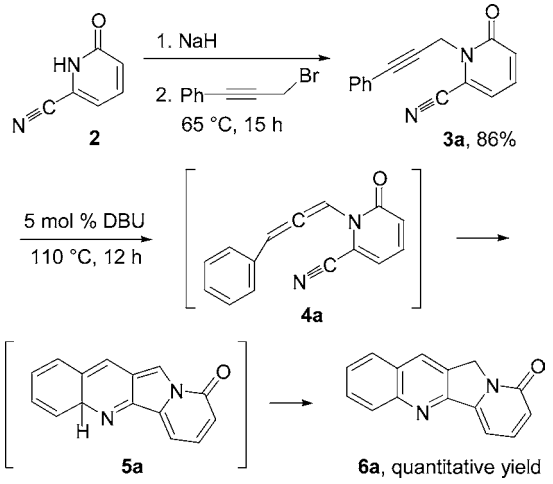
(3) Saltz, L. B. In *Colorectal Cancer*; Saltz, L. B., Ed.; Humana Press, Inc.: Totowa, 2002; pp 513−524.

10.1021/ol0620242 CCC: $33.50
Published on Web 09/07/2006

CD ring core.[6] We now report the use of the chemically more robust nitrile group to replace the chemically labile isonitrile group in a conjugated system to produce the parent and substituted ABCD ring cores in a single cascade sequence.

The synthetic sequence involved the *N*-alkylation of **2**, readily prepared from either 2-bromo- or 2-chloro-6-methoxypyridine,[7] with 3-bromo-1-phenylpropyne using Curran's protocol[8] to produce 1,6-dihydro-6-oxo-(3-phenyl-2-propynyl)-2-pyridinecarbonitrile (**3a**) in 86% yield (Scheme 1).

Scheme 1



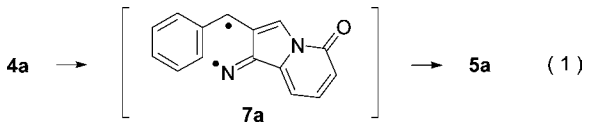
Treatment of **3a** with a catalytic amount of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU, 5 mol %) in 1,2-dichlorobenzene at 110 °C for 12 h produced indolizino[1,2-*b*]quinolin-9-(11*H*)-one (**6a**),[7a,9] the parent ABCD ring core of camptothecin, in essentially quantitative yield. In the absence of DBU, no reaction occurred and **3a** was recovered. With 1 equiv of DBU, the reaction was complete within 2 h at 120 °C. Presumably, the transformation from **3a** to **6a** involved an initial 1,3-prototropic rearrangement to form the corresponding allenic intermediate **4a**. A subsequent intramolecular hetero Diels−Alder reaction to form **5a** followed by a second prototropic rearrangement to regain aromaticity then produced **6a**.

The use of a base, such as potassium *tert*-butoxide or sodium hydroxide, to promote the acetylene−allene rearrangement of *N*-substituted propargyl amides has been reported previously.[10] This process was employed in generating a benzannulated enyne−allene system for subsequent transformation to an indeno-fused 4*H*-quinolizin-4-one.[10a] However, initial attempts to use potassium *tert*-butoxide resulted in complete consumption of **3a** but without the formation of **6a**. Exposure of **3a** to triethylamine in 1,2-dichlorobenzene at 120 °C for 27 h produced only a small quantity of **6a** while large portions of **3a** remained unreacted. The success of DBU in catalyzing the reaction may be attributed to its stronger basicity than that of triethylamine[11] but gentler nature than potassium *tert*-butoxide.

The involvement of the nitrile group in the apparent intramolecular hetero-Diels−Alder reaction of **4a** is worth mentioning. Unactivated nitriles are known to be very resistant to the Diels−Alder reactions.[12] However, electron-deficient nitriles, such as *p*-toluenesulfonyl cyanide and ethyl cyanoformate, are good dienophiles, capable of undergoing Diels−Alder reactions at ambient temperature.[12] The nitrile group in **4a** is in conjugation with the 2(1*H*)-pyridone system, presumably making it more reactive for the Diels−Alder reaction. The involvement of an allenic moiety as a part of the diene component may also enhance the propensity for the Diels−Alder reaction.[13]

The use of the intramolecular hetero-Diels−Alder strategy as an efficient way to construct the BC rings of camptothecins has previously been demonstrated in a formal synthesis of camptothecin involving the cycloaddition reaction between an *N*-arylimidate and an unactivated alkyne as a key step.[14] The intramolecular cycloaddition reaction between an *N*-arylimine and an unactivated alkyne has also found success in the synthesis of a camptothecin precursor.[15] In these two cases, the heteroatom is on the diene component. Our approach of using a nitrile group for intramolecular cycloaddition with an arylallenic moiety is unique in that the heteroatom is on the dienophile.

An alternative mechanism to the concerted Diels−Alder reaction in producing **5a** may involve a stepwise mechanism with the formation of biradical **7a** from **4a** followed by an intramolecular radical−radical coupling to give **5a** (eq 1).



(1)

There are ample precedents in the literature for the analogous

(4) (a) Berry, D. E.; MacKenzie, L.; Shultis, E. A.; Chan, J. A.; Hecht, S. M. *J. Org. Chem.* **1992**, *57*, 420−422. (b) Fang, S.-D.; Wang, L.-K.; Hecht, S. M. *J. Org. Chem.* **1993**, *58*, 5025−5027.

(5) Perzyna, A.; Marty, C.; Facompré, M.; Goossens, J.-F.; Pommery, N.; Colson, P.; Houssier, C.; Houssin, R.; Hénichart, J.-P.; Bailly, C. *J. Med. Chem.* **2002**, *45*, 5809−5812.

(6) Lu, X.; Petersen, J. L.; Wang, K. K. *Org. Lett.* **2003**, *5*, 3277−3280.

(7) (a) Bowman, W. R.; Bridge, C. F.; Brookes, P.; Cloonan, M. O.; Leach, D. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 58−68. (b) Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, J.; Weiss, S.; Beller, M. *Chem. Eur. J.* **2003**, *9*, 1828−1836.

(8) Liu, H.; Ko, S.-B.; Josien, H.; Curran, D. P. *Tetrahedron Lett.* **1995**, *36*, 8917−8920.

(9) (a) Kametani, T.; Nemoto, H.; Takeda, H.; Takano, S. *Tetrahedron* **1970**, *26*, 5753−5755. (b) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1992**, *114*, 5863−5864. (c) Nguyen, T.; Wicki, M. A.; Snieckus, V. *J. Org. Chem.* **2004**, *69*, 7816−7821.

(10) (a) Dai, W.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2005**, *70*, 6647−6652. (b) Grigg, R.; Köppen, I.; Rasparini, M.; Sridharan, V. *Chem. Commun.* **2001**, 964−965. (c) Grigg, R.; Loganathan, V.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1996**, *52*, 11479−11502.

(11) Kaljurand, I.; Kütt, A.; Sooväli, L.; Rodima, T.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019−1028.

(12) (a) McClure, C. K.; Link, J. S. *J. Org. Chem.* **2003**, *68*, 8256−8257 and references therein. (b) Li, W.-T.; Lai, F.-C.; Lee, G.-H.; Peng, S.-M.; Liu, R.-S. *J. Am. Chem. Soc.* **1998**, *120*, 4520−4521 and references therein.

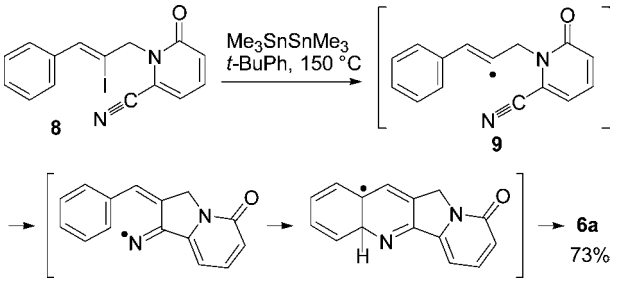
(13) Keck, G. E.; Kachensky, D. F. *J. Org. Chem.* **1986**, *51*, 2487−2493.

(14) Fortunak, J. M. D.; Mastrocola, A. R.; Mellinger, M.; Sisti, N. J.; Wood, J. L.; Zhuang, Z.-P. *Tetrahedron Lett.* **1996**, *37*, 5679−5682.

(15) Twin, H.; Batey, R. A. *Org. Lett.* **2004**, *6*, 4913−4916.

benzannulated enyne−allene system[16] and aza-analogues[17] to form the corresponding benzofulvene and related biradicals under thermal conditions. A similar benzannulated enallene−nitrile case was also reported,[18] although other examples failed to generate biradicals.[19] The use of **8** to generate radical **9** for the radical cyclization reactions was found to be successful in producing **6a** (Scheme 2).[7a] A radical reaction

Scheme 2

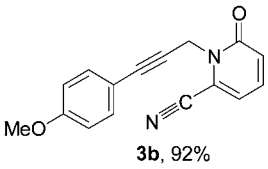
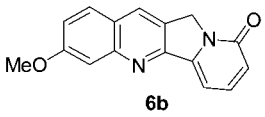
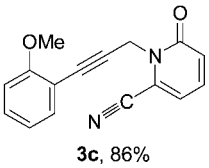
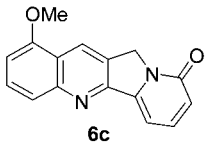
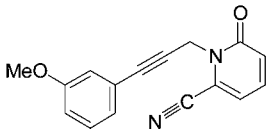
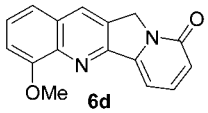
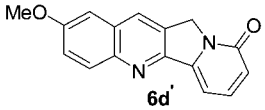
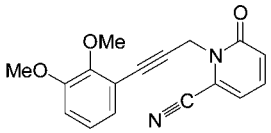
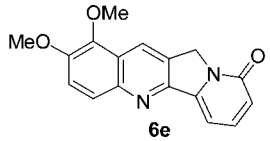


pathway involving phenyl isonitrile and a 2-pyridonyl radical was also reported for the construction of the ABCD ring core.[20]

By using the propargyl bromides having one or two methoxyl groups on the phenyl substituent at the alkynyl terminus and again employing Curran's protocol for the *N*-alkylation with **2**, four different 2(1*H*)-pyridones **3b**−**e** were obtained (Table 1). Treatment of **3b** with 1 equiv of DBU at 120 °C gave the only possible product **6b** within 2 h in essentially quantitative yield. A single product **6c**[7a] was also derived from **3c**. Apparently, the Diels−Alder reaction or the intramolecular radical−radical coupling step did not involve the ortho carbon bearing the methoxyl group. However, in the case of **3d**, a mixture of the regioisomers **6d** and **6d′**[14] (4:3) was produced. The structure of **6d** was established by X-ray structure analysis. With an *o*-methoxy substituent again present in the case of **3e**, a single isomer **6e** was obtained.

In conclusion, a new synthetic pathway to the parent and substituted ABCD ring cores of the camptothecin family of alkaloids was developed. The need to use only DBU to induce the cyclization process producing essentially quantitative yields of the cyclized adducts under mild thermal conditions is particularly attractive. The convergent synthetic

Table 1. Synthesis of 1-(3-Aryl-2-propynyl)-1,6-dihydro-6-oxo-2-pyridinecarbonitriles and Indolizino[1,2-*b*]quinolin-9-(11*H*)-ones

1-(3-aryl-2-propynyl)-1,6-dihydro-6-oxo-2-pyridinecarbonitriles	indolizino[1,2-*b*]quinolin-9(11*H*)-ones[a]
 **3b**, 92%	 **6b**
 **3c**, 86%	 **6c**
 **3d**, 84%	 **6d**  **6d′** (**6d** : **6d′** = 4 : 3)
 **3e**, 76%	 **6e**

[a] Quantitative yields.

sequence also allows easy placement of a variety of substituents on the ABCD ring core.

Acknowledgment. The financial support of the National Science Foundation (CHE-0414063) is gratefully acknowledged. K.K.W. thanks the National Science Council of Taiwan, the Republic of China, for a grant to support sabbatical leave in the Department of Chemistry at the National Taiwan University. J.L.P. acknowledges the support (CHE-9120098) provided by the National Science Foundation for the acquisition of a Siemens P4 X-ray diffractometer. The financial support of the NSF-EPSCoR (1002165R) for the purchase of a 600 MHz NMR spectrometer is also gratefully acknowledged.

Supporting Information Available: Experimental procedures, spectroscopic data, and ^{1}H and/or ^{13}C NMR spectra of 3-(2,3-dimethoxyphenyl)-2-propyn-1-ol, 3-bromo-1-arylpropynes, **3a**−**e**, and **6a**−**e**; ORTEP drawings of the crystal structures of **3b**, **6a**, and **6d**; and X-ray crystallographic data of **3b**, **6a**, and **6d** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL0620242

(16) (a) Schmittel, M.; Strittmatter, M.; Vollmann, K.; Kiau, S. *Tetrahedron Lett.* **1996**, *37*, 999−1002. (b) Schmittel, M.; Strittmatter, M.; Kiau, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1843−1845. (c) Schmittel, M.; Vavilala, C. *J. Org. Chem.* **2005**, *70*, 4865−4868.

(17) Li, H.; Yang, H.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2004**, *69*, 4500−4508 and references therein.

(18) Wu, M.-J.; Lin, C.-F.; Chen, S.-H.; Lee, F.-C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2875−2876.

(19) (a) Wang, K. K.; Wang, Z.; Sattsangi, P. D. *J. Org. Chem.* **1996**, *61*, 1516−1518. (b) Gillmann, T.; Heckhoff, S. *Tetrahedron Lett.* **1996**, *37*, 839−840.

(20) Curran, D. P.; Liu, H.; Josien, H.; Ko, S.-B. *Tetrahedron* **1996**, *52*, 11385−11404.