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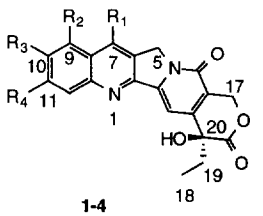
Novel Syntheses of Camptothecin Alkaloids, Part I. Intramolecular [4+2] Cycloadditions of N-Arylimidates and 4H-3,1-benzoxazin-4-ones as 2-Aza-1,3-Dienes

Joseph M.D. Fortunak,* Antonietta R. Mastrocola, Mark Mellinger, Nicolas J. Sisti, Jeffery L. Wood and Zhi-Ping Zhuang

Chemical Process R&D, DuPont Merck Pharmaceutical Co.,
Chambers Works, PRF(S1) Deepwater, NJ 08023-0999

Department of Synthetic Chemistry, SmithKline Beecham Corporation,
709 Swedeland Road, King of Prussia, PA 19406-0939

Abstract: The first reported intramolecular [4+2] cycloadditions of both N-arylimidates and 4**H**-3,1-benzoxazin-4-ones acting as 2-aza-1,3-dienes are described. Reaction with unactivated alkynes leads to pyrrolo[3,4-b]quinolines which constitute the ABC ring system of camptothecins. Copyright © 1996 Elsevier Science Ltd



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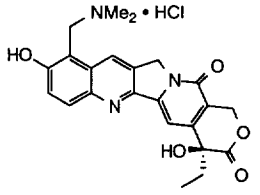

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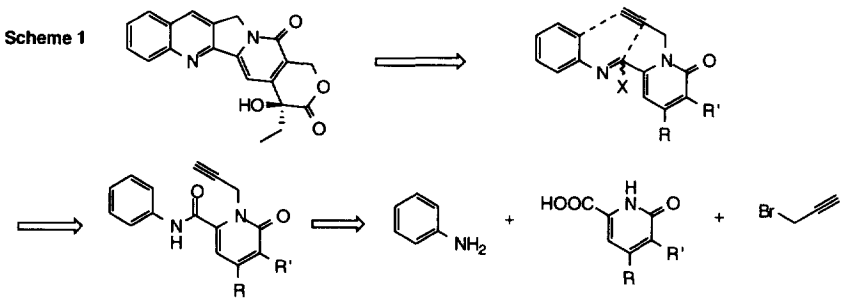
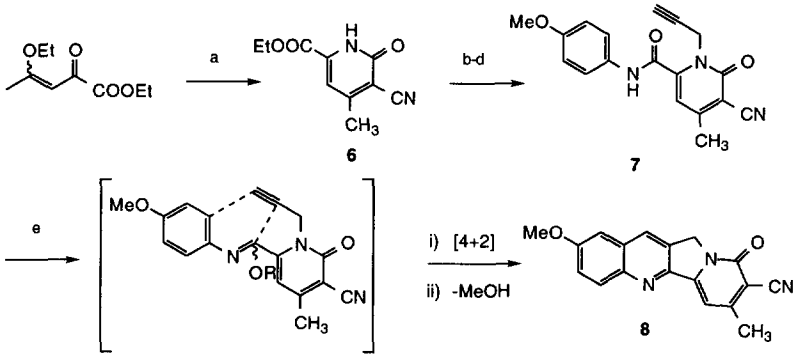
1	R_1 - R_4 = H	Camptothecin
2	R_1 = C_2H_5, R_3 = OCO-(4-piperidinyl piperidine)	Irinotecan(Daiichi/Yakult)
3	R_3-R_4 = ethylenedioxy R_1 = CH_2(N-Me-piperazine)	GI-147211C(Glaxo)
4	R_2 = NH_2	9-aminocamptothecin(NCI)
5	as shown	Topotecan(SmithKline Beecham)

Camptothecin[1] is a selective inhibitor of mammalian topoisomerase I[2,3] originally isolated from the Chinese tree *Camptotheca acuminata*. A number of camptothecin analogues (**2-5**) are being developed as anticancer agents.[4,5] Several intriguing total syntheses of camptothecin have been published[6] of which perhaps the most commercially viable originate from the Comins group.[7] With the recent FDA marketing approval of topotecan (**5**)[4a] we wish to report some of our efforts from the SmithKline Beecham process chemistry group in this area. Scheme 1 indicates our retrosynthetic strategy used to synthesize camptothecin and various of its analogues, including topotecan. We assembled the pyrrolo[3,4-b]quinoline ring system (ABC rings) of camptothecins by the previously unknown, intramolecular [4+2] cycloaddition of unactivated alkynes with either N-arylimidates or 4**H**-3,1-benzoxazin-4-ones (Schemes 2 and 3). ABCD ring precursors of camptothecins were therefore prepared from the appropriate aniline, a propargyl unit, and various 2-pyridone-6-carboxylic acids.

Scheme 1



Scheme 2 illustrates our initial success. The 2-(1**H**)-pyridone **6**[6a] was converted in three steps to **7** in 51% overall yield. Stirring of **7** with three equivalents of trimethyloxonium fluoroborate in methylene chloride solution at 20 °C gave the corresponding O-methylimidate (4:1 mixture of stereoisomers, major isomer not determined) indicated by ^{1}H NMR spectroscopy. The desired, intramolecular [4+2] cycloaddition and subsequent elimination of methanol did occur, albeit slowly, under these conditions. Replacement of the solvent with acetonitrile and refluxing for six hours gave a single major product (analytical TLC/HPLC). The product was isolated by concentration of the solvent and crystallization from hot methanol to give the tetracyclic quinoline **8** in 82% yield from **7**.[8] This amounts to a formal total synthesis of (±) 10-methoxycamptothecin.[6b,c]

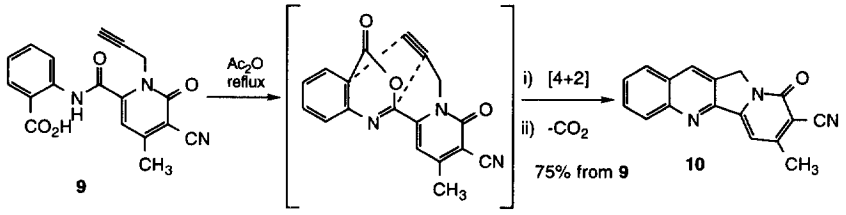


Scheme 2 Reagents and Conditions: a) cyanoacetamide, K_2CO_3, acetone, reflux; 82% b) propargyl bromide, DMF, K_2CO_3 ; 65% c) NaOH, aq. DMF; 95% d) *p*-anisidine, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide:HOBT, CH_2Cl_2; 83% e) CH_2Cl_2, Me_3OBF_4, RT °; followed by CH_3CN, reflux; 82%

The formation of **8** is effectively the intramolecular [4+2] cycloaddition of an "electron-neutral" alkyne with a 2-aza-1,3-diene, with the aryl ring serving as a 2π component of the diene. Although the intramolecular cycloaddition of 2-azadienes has been reported[9] and, in special circumstances, N-arylimines and N-arylimmonium salts have been condensed in a [4+2] fashion with electron-rich olefins[10-12] we believe this to be the first report of N-arylimidates serving as 4π components in a Diels-Alder reaction.[13]

In some cases cycloaddition through the intermediate imidate gave poor yields. This was dependent upon the substitution pattern on the aromatic ring and the stability of the imidate towards competitive rearrangement[13] and/or decomposition. Substrates with at least one electron-donating substituent (*e.g.*, methoxy) on the aromatic ring gave good yields of product. When yields are poor, a preferred alternative is cycloaddition through the analogous 4**H**-3,1-benzoxazin-4-one.[14] Benzoxazinone **9** in Scheme 3 was derived from **6** by ester hydrolysis followed by coupling with anthranilic acid (CDI in THF, 88% yield after recrystallization). Ring closure to form the benzoxazinone in refluxing acetic anhydride[15] also resulted in intramolecular cycloaddition and loss of carbon dioxide to give the corresponding quinoline. Tetracycle **10** was

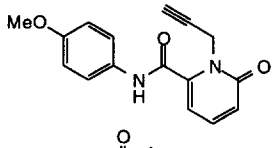
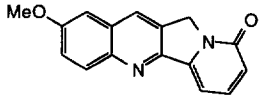
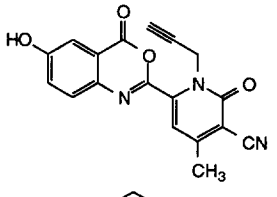
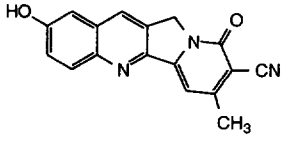
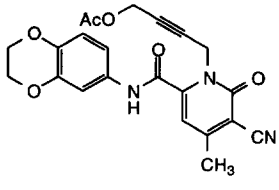
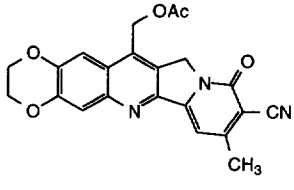
obtained in 75% yield (*cf.* Scheme 3) from **9** in this manner. The conversion of **10** to racemic camptothecin is known.[6b,c] The only analogous reaction of benzoxazinones is their stepwise [4+2] addition with ynamines, giving rise to quinolines with narrowly restricted substitution patterns.[16]



Scheme 3

We have not extensively examined the reactions of N-arylimidates or 4H-3,1-benzoxazin-4-ones with a range of dienophiles. A few additional intramolecular cycloadditions are listed in the Table below. Our current results are consistent with the products being formed through a [4+2] cycloaddition, although the possibility of either reaction occurring through a stepwise mechanism has not been rigorously disproven. We have used this strategy to carry out total syntheses of compounds **1-3** and **5**. A concise total synthesis of camptothecin analogues, including (S)-topotecan (**5**) is described in the communication immediately following.[17]

TABLE

Substrate	Method (yield)	Product
	A (65%)	
	B (74%)	
	A (48%)	

Method A : 3 eq. trimethyloxonium tetrafluoroborate; acetonitrile, 20 °C followed by reflux
Method B : reflux in acetic anhydride

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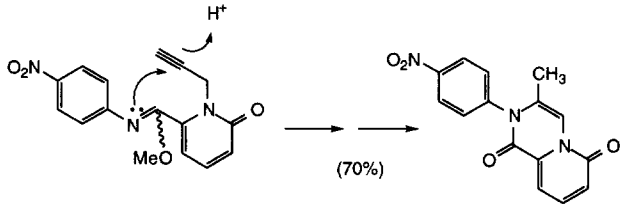
13. Since formation of the imidate produces one mole equivalent of fluoroboric acid this reaction is likely an inverse electron-demand [4+2] cycloaddition of the protonated azadiene with the "electron-rich" alkyne. The reaction occurs, although more slowly, through the neutral imidate. Photolysis, radical traps or initiators have no significant effect on the reaction. The benzoxazinones react uniformly in a [4+2] fashion whereas the p-nitro-N-arylimidate reacts as below, giving the desired cycloaddition in poor yield (15-20%; compare with ref. 10). Lewis acid catalyzed reaction of various imidates or reaction through the O-silyl-imidates also gives primarily the reaction pathway indicated below.



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17. A preliminary, partial disclosure of this work was first presented at the University of New Orleans, February 21, 1992.

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