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Total synthesis of a novel non-lactone camptothecin analog through microwave-assisted [3,3]-sigmatropic rearrangement

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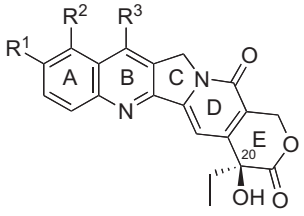
ABSTRACT

A novel, flexible synthesis of a non-lactone camptothecin analog has been accomplished concisely with a microwave-assisted sigmatropic rearrangement as the key step.

1. Introduction

Camptothecin (CPT) (**1**, Fig. 1) is a powerful antitumor alkaloid, first isolated from the leaves of the Chinese bush *Camptotheca acuminata* by Wall and co-workers in 1966.[1] Its cytotoxicity is related to its ability to stabilize the covalent binary complex formed between DNA and topoisomerase I (topo I), an enzyme essential for the relaxation of DNA.[2] Two water soluble analogs, topotecan (**2**, Hycamtin)[3] and irinotecan (**3**, Camptosar)[4] are currently used clinically for the treatment of ovarian and colon cancers, respectively.



1 $R^1 = R^2 = R^3 = H$ (Camptothecin)
2 $R^1 = OH$, $R^2 = CH_2NMe_2.HCl$, $R^3 = H$ (Topotecan)
3 $R^1 = OCOPipPip$, $R^2 = H$, $R^3 = Et$ (Irinotecan)

Fig. 1. Camptothecin and analogs.

Over the years, most SAR studies of camptothecin have been conducted with AB-modified CPT that possess the intact E-ring, since it was long believed that the α-hydroxy lactone was essential for the biological activity.[5] However, there exists an intrinsic chemical instability in these derivatives due to the presence of this hydroxy lactone: under physiological conditions, a rapid E-ring-opening occurs to produce the corresponding open carboxylate derivative with consequent loss of therapeutic efficacy.[6] Unfortunately, the early E-ring modifications to improve the chemical stability of these compounds had produced either inactive or less active derivatives, engendering the above-mentioned belief that clinically potent candidates could not be secured through this strategy. However, in 1997, Lavergne and co-workers reported that homocamptothecin (**4**, Fig. 2), with a methylene spacer between the tertiary hydroxyl and the lactone carbonyl, manifested improved lactone stability, higher cytotoxicity, and enhanced topoisomerase I inhibition.[7] A number of homocamptothecin analogs have since been prepared and bioevaluated and two (**5** and **6**) are currently in clinical trials.[8,9]

The success of these new drugs raised the possibility that other modifications of the E-ring might also lead to active compounds.[10] This has proven to be correct: recently, even non-lactone analogs (**7**–**10**, Fig. 2) have been shown to possess interesting pharmacological properties and S39365 (**8**) is currently in preclinical development.

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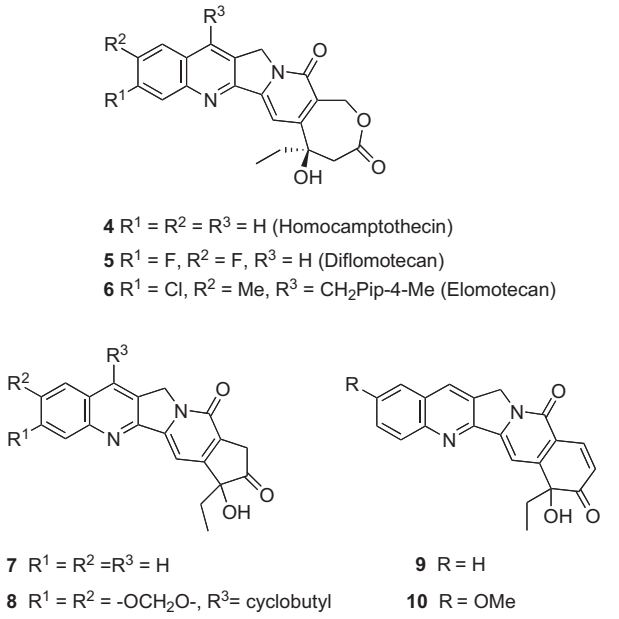
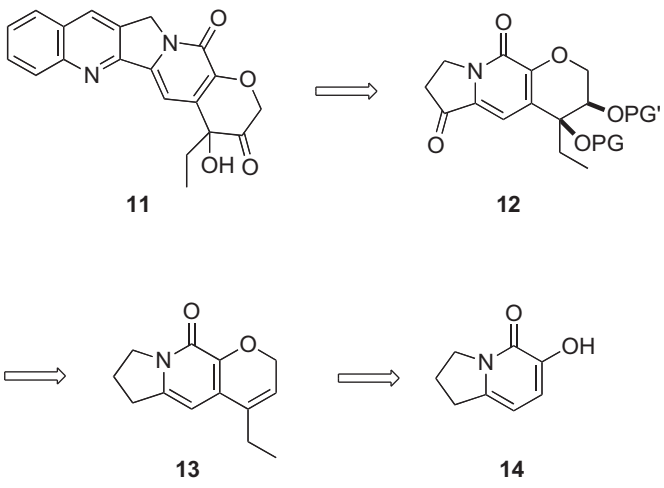


Fig. 2. Structures of homocamptothecins and non-lactone camptothecin analogs.

In connection with a research program focused on the synthesis of camptothecin and derivatives,[11] we have realized the total synthesis of the novel non-lactone camptothecin analog **11** (Scheme 1), which is isomeric with the natural alkaloid (translocated endocyclic oxygen). We report its synthesis herein.

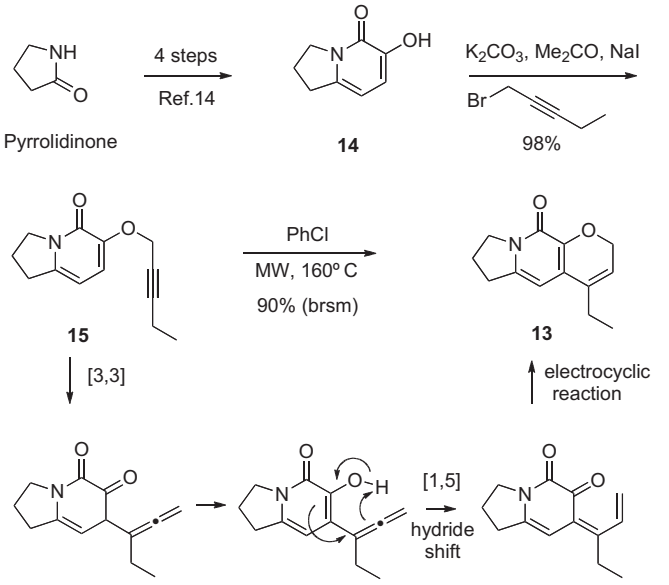


Scheme 1. Retrosynthesis of camptothecinoid **11**.

Our synthetic plan relied on a Friedländer condensation[12] of a key pyrrolidinone **12**, which seemed accessible from tricycle **13** by sequential cis dihydroxylation of the double bond, hydroxyl protection, and oxidation of the pseudo benzylic position on the pyrrolidine ring (Scheme 1). Intermediate **13**, in turn, might be readily accessed from the known hydroxy pyridone **14** through a [3,3] sigmatropic rearrangement.[13]

2. Results and discussion

The starting hydroxy pyridone **14** was obtained in high yield as previously described by Padwa and co-workers.[14] It was then *O*-propargylated in nearly quantitative yield with 1-bromo-2-pentyne in the presence of anhydrous potassium carbonate and a small amount of sodium iodide to provide ether **15** (Scheme 2).



Scheme 2. Synthesis of tricycle **13**.

In order to promote the Claisen rearrangement of **15**, it was heated in refluxing chlorobenzene for 22 h. The desired pyrane derivative **13** was indeed obtained, albeit in a modest 45% yield (80% brsm). Extended reaction times or changing the solvent to DMF were not beneficial and only produced additional decomposition. It was found, however, that this transformation could be substantially improved through microwave irradiation. Heating **15** in a sealed tube with microwave irradiation for just 1 h produced the pyrane derivative **13** in 68% yield (90% yield brsm). This key transformation probably involves Claisen rearrangement, enolization, and cyclization, as detailed in Scheme 2. It should be pointed out that this cyclization represents a rare example of a Claisen rearrangement of a pyridone propargyl ether derivative.[15]

With the tricycle **13** in hand, its functionalization to obtain the Friedländer precursor was next examined (Scheme 3). First, dihydroxylation was performed by using a catalytic amount of OsO_4 in the presence of $K_3Fe(CN)_6$. The expected racemic[16] diol **16**, obtained in excellent yield, was next protected as its acetonide by reaction with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid in DMF (75% yield). The protected diol was then treated with selenium dioxide in refluxing dioxane to provide the expected alcohol **17** in 91% yield. Finally, ketone **18** was obtained cleanly from **17** through treatment with Dess–Martin periodinane (DMP) in dichloromethane.

This ketone was directly engaged in the Friedländer condensation with the Borsche imine (**19**) and a catalytic amount of pyridinium *p*-toluenesulfonate in refluxing toluene to give quinoline **20** in 65% yield (two steps). On treatment with *p*-toluenesulfonic acid in refluxing methanol, the quinoline was converted into the corresponding diol **21** in quantitative yield. At this stage, a mild oxidation was required in order to transform the secondary hydroxyl into a carbonyl, without diol cleavage occurring, to obtain the desired camptothecinoid **11**.

The effectiveness of hypervalent iodine reagents,[18] such as IBX[19] and DMP,[20] in this type of transformation is well recognized. To our dismay, though, despite many attempts (with excess oxidant, high temperature, prolonged reaction times, different solvents, and/or ionic liquids) to achieve this conversion, diol **21** completely resisted transformation with these oxidants. Fortunately, however, the diol