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# Preparation of Mappicine Ketones from Camptothecins: Chemistry of the Camptothecin E Ring

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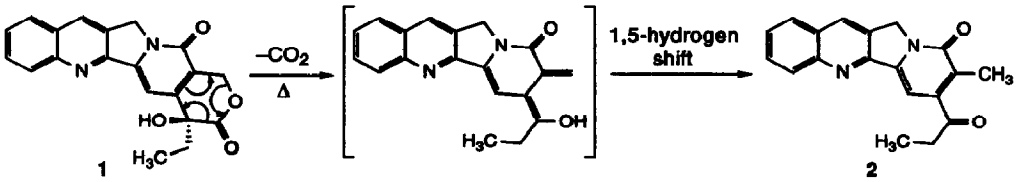
***Abstract:*** *Camptothecin and its analogs are thermolyzed at 150-200 °C to yield mappicine ketone derivatives by loss of carbon dioxide from the α-hydroxylactone.*

Topoisomerase I and II are enzymes which alter DNA topology, allowing it to unwind as a prelude to strand scission and replication. The alkaloid camptothecin (**1**)[1] is a topoisomerase I inhibitor[2] which shows outstanding antineoplastic activity in animal tumor models.[3] Analogs of **1** are undergoing clinical investigation as human chemotherapeutic agents. Mappicine ketone (**2**) and mappicine (**2**, ketone reduced to S-alcohol) are natural products formally related to camptothecin by the loss of carbon dioxide.[4] Derivatives of these molecules are of interest as selective inhibitors of topoisomerase II.

Although camptothecin is available in quantity from the biomass of both *Camptotheca acuminata* and *Nothapodytes foetida*, **2** and **3** are present only in *N. foetida* extracts, and their low abundance prohibits isolation of meaningful amounts.[1,5] We disclose here the convenient, high-yield transformation of camptothecin and several readily available analogues into mappicine ketones. This makes available multigram quantities of compounds, related to **2** and **3**, which are of interest in medicinal and pharmacological research.

A previously-reported[6] conversion of camptothecin to mappicine ketone required azide ion for E-ring cleavage, which was followed by expulsion of carbon dioxide and loss of azide. This reaction gave sharply lower yields when it was scaled past 50 mg and it failed completely when applied to analogs of camptothecin.

We have found that camptothecin can be converted directly to mappicine ketone by the direct extrusion of carbon dioxide on heating to >150 °C (Scheme 1). The reaction is clean and selective, can be scaled up without loss of yield, and appears to be general for camptothecin analogs bearing the intact α-hydroxylactone ring.




**Scheme 1**

Camptothecin is converted cleanly to mappicine ketone (>95% solution yield)[7] on extended reflux in N,N-dimethylformamide (153 °C). After cooling to 23 °C, the precipitated product is isolated by filtration in yields of 88-93% on reaction scales of 5-50 grams. Changing the solvent to triglyme at 200 °C gives a shorter reaction time (6 h) and allows the successful application of the reaction to substituted camptothecins (Table).[8]

This reaction is apparently limited to analogs with an intact α-hydroxylactone. 20-Chlorocamptothecin rearranges at 130 °C in DMF to give a semi-anhydride, presumably through elimination of hydrogen chloride followed by the 1,6-addition of water (Scheme 2). Although this product can be isolated in 75% yield at 130 °C, decomposition is seen at higher temperatures. 20-*Des*-hydroxycamptothecin[1] is unchanged on heating to approximately 220 °C, at which point slow decomposition to form several products occurs.

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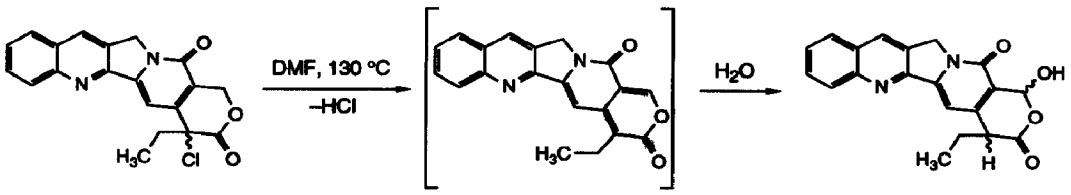
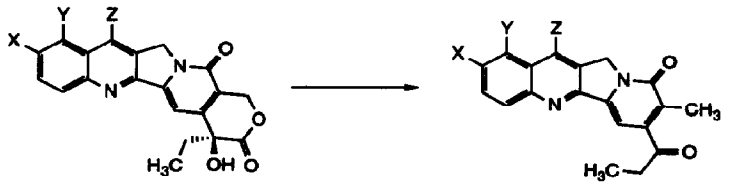



**Scheme 2**

**Table**



| Starting Material | Conditions[a] | Isolated Yield | Product[9] |
|---|---|---|---|
| X, Y, Z=H | DMF, 192 h | 93% | mappicine ketone (MPK) |
| | triglyme, 6 h | 92% | MPK |
| X=OH; Y, Z=H | triglyme, 6.5 h | 95% | 10-hydroxy-MPK |
| X=OMe; Y, Z=H | triglyme, 9 h | 82% | 10-methoxy-MPK |
| X=OH; Y=H; Z=Et | triglyme, 9.5 h | 77% | 7-ethyl-10-hydroxy-MPK |
| X, Z=H; Y=OMe | triglyme, 9.5 h | 79% | 9-methoxy-MPK |

a. Reactions in DMF heated at 153 °C; reactions in triglyme heated at 200 °C.

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**References and Notes**

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7. Reactions were monitored by HPLC using a Waters $C_{18}$ μBondapak column and aqueous 0.1 M ammonium dihydrogen phosphate (adjusted to pH 3.0 with triethylamine) mixed 77:23 with acetonitrile:. The relative retention time of mappicine ketone is approximately 2.0 vs. camptothecin under these conditions.
8. A typical experiment follows: A suspension of 50.0 g of camptothecin (Atul Corporation, ~97% pure) in 500 mL of triglyme (Aldrich, 99%, used as received) was stirred under nitrogen while heating to an internal temperature of 200 °C. The disappearance of starting material was monitored by HPLC.[7] Complete solution was achieved at a temperature of about 140 °C. After 6 hours only about 1% starting material remained and the reaction was allowed to cool to 23 °C with stirring over several hours. The resulting suspension was diluted with 500 mL of diethyl ether and the product was collected by filtration. After being washed with 250 mL of diethyl ether and dried to a constant weight under vacuum (<0.1 mm Hg) at 45 °C, the isolated product weighed 39.1 g and had spectral and physical properties identical to those of authentic mappicine ketone. The yield was 92% corrected for purity (99.3% by HPLC assay against a reference standard).
9. All new compounds were characterized by IR, NMR and Mass Spectroscopy (including exact mass determination) as well as elemental analysis.

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