Novel, efficient total synthesis of natural 20(*S*)-camptothecin†

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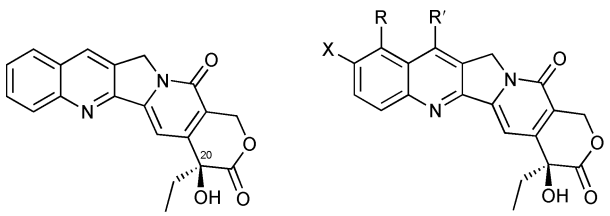
Enantiopure 20(*S*)-camptothecin has been prepared from a known hydroxypyridone through a novel approach that involves a Claisen rearrangement, an asymmetric nucleophilic ethylation, a Heck coupling and a Friedländer condensation as the key transformations.

Camptotheca acuminata is a tree indigenous to China, where it is known as xi shu and used in traditional medicine for a wide spectrum of symptoms.[1] Camptothecin (**1**) (Fig. 1), present in the fruit, bark, and wood of this plant, was first isolated by Wall and colleagues in 1958 from its stem wood and structurally elucidated a few years later.[1–3]

Preclinical studies of this alkaloid in leukemia and carcinosarcoma models proved promising, but its general insolubility subsequently generated a number of problems, as well as misleading results. However, later elucidation of its *in vivo* lactone chemistry and novel mechanism of action, which involves the selective inhibition of DNA topoisomerase I, rekindled the initial excitement and has led to several syntheses of camptothecin, as well as to the preparation of a number of more soluble congeners. Two such analogs, Irinotecan (**2a**) and Topotecan (**2b**), are now commercially available (ovarian, cervical, colon, colorectal, and lung cancers) and several others are presently in preclinical and clinical trials.[4,5]



1, Camptothecin

2a, Irinotecan
(X = OCOPipPip, R = H, R′ = Et)
2b, Topotecan
(X = OH, R = CH_2NMe_2 , R′ = H)

Fig. 1 Camptothecin (**1**), Irinotecan (**2a**), and Topotecan (**2b**).

Published asymmetric syntheses of these molecules have involved a number of different approaches for introducing the 20(*S*) configuration, which include the use of chemical and enzymatic resolutions,[6] chiral pool-derived precursors,[7] chiral auxiliaries,[8] and asymmetric hydroxylation and dihydroxylation reactions.[9] Most surprisingly, however, asymmetric nucleophilic ethylation of an α-keto ester (or lactone) derivative has yet to be exploited for this purpose, in spite of the fact that adjacency of an aromatic ring or an alkoxycarbonyl group tends to impact favorably on asymmetric addition to keto and aldehydic carbonyls.[10] In this paper an effective asymmetric synthesis of natural 20(*S*)-camptothecin through the use of such a strategy is disclosed.

We have recently illustrated a modular approach to racemic and achiral camptothecinoids from the Padwa hydroxypyridone[11] that is based in part on a Claisen rearrangement and a Friedländer condensation.[12] These are adaptable, highly versatile transformations that have been retained in our asymmetric approach, which is outlined retrosynthetically for camptothecin in Chart 1. The natural product was to be secured by deprotection of the Friedländer product derived from condensation of keto pyridone **II**, obtained by oxidation of pyridone **I**. The elements necessary for the construction of this chiral hydroxy lactone derivative would be introduced by a Claisen rearrangement for the β substituent and a Heck coupling for the α substituent, starting from the Padwa hydroxypyridone **3**, which is readily prepared through isomünchnone cycloaddition chemistry.[13]

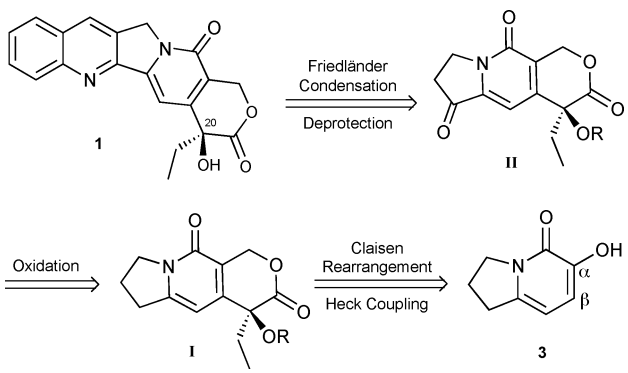


Chart 1 Retrosynthesis of camptothecin (**1**).

Hydroxypyridone **3** was obtained in high yield from 2-pyrrolidinone, as previously described,[11] and then converted into crotonate **4** in 96% yield through reaction with methyl 4-bromocrotonate (Scheme 1). The crotonate rearranged smoothly in hot *o*-dichlorobenzene (DCB) to give the β,γ-unsaturated ester Claisen product,[14] which without purification was isomerized through exposure to piperidine at 20 °C to provide the acrylate derivative **5a** (84%, 2 steps).

To cleave oxidatively the ethylidene group in **5a**, it proved necessary to first deactivate the hydroxypyridone moiety by triflation (98%); this permitted the desired scission to proceed selectively with ozone in dichloromethane at −90 °C to give keto ester **6** in 96% yield. With this keto ester in hand, the key asymmetric nucleophilic ethylation was next undertaken. The method recently described by DiMauro and Kozlowski[15] provided

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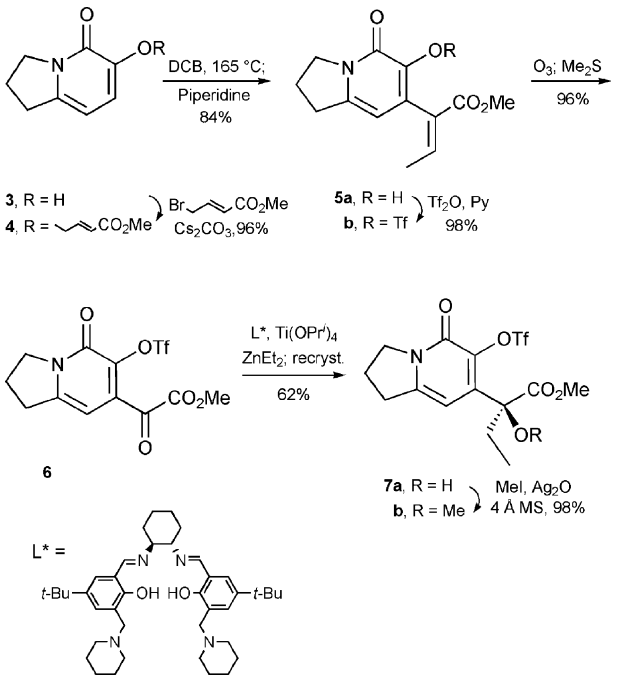
† Electronic supplementary information (ESI) available: Experimental description and product characterization data for the conversion of **3** into **1**. See DOI: 10.1039/b611202a



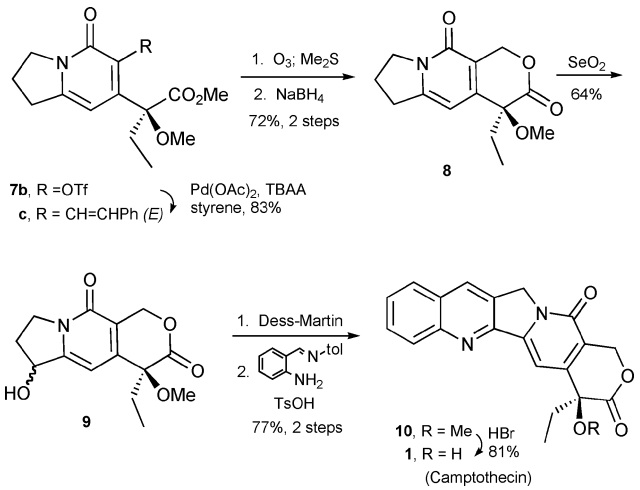
Scheme 1 Synthesis of enantiopure ester **7b**.

an exceptionally pleasing result: a 95% conversion of **6** and an ee of **7a** of 90%.[16] Equally pleasing was that simple recrystallization of the product provided pure material (>99% ee, 62% overall yield). To the best of our knowledge, this is the first application of this effective method in natural product synthesis.

Methyl ether protection of the C-20 hydroxyl was chosen over other possible forms of protection, since it had earlier been found in our racemic synthesis[12b] that camptothecin could be efficiently obtained from its methyl ether with hot hydrobromic acid and, in addition, shown in a control experiment that natural camptothecin was configurationally stable to these deprotection conditions.[17,18] The conversion of **7a** into its methyl ether proved, however, to be unexpectedly challenging. After several unrewarding attempts, it was discovered that the conditions recently described by Eustache and coworkers[19] led in nearly quantitative yield to the desired methyl ether **7b**, an intermediate in our racemic synthesis, but now in enantiopure form.

The concluding steps of the synthesis of natural camptothecin closely paralleled those used for the racemic product (Scheme 2). First, lactone construction to afford **8** was readily accomplished by Heck coupling[20] of **7b**, followed by oxidative cleavage of the resultant styryl derivative and reduction. The quinoline rings were next grafted onto lactone **8** to give the methyl ether of camptothecin (**10**) through oxidation at the benzylic-like site and then Friedländer condensation[21] with an *o*-aminobenzaldehyde surrogate.[22] Finally, 20(*S*)-camptothecin (**1**) was obtained from its methyl ether in high yield and, as expected, without a trace of racemization by exposure to hot hydrobromic acid. The synthetically derived material ($[\alpha]^{20}_D$ +40 (*c* 0.2 in 1 : 4 MeOH : $CHCl_3$), mp 260–264 °C, dec.) was spectroscopically and chromatographically identical with a sample of naturally derived camptothecin.[23]

In conclusion, a new synthesis of 20(*S*)-camptothecin has been developed that is both efficient and flexible. An intramolecular version of the approach is currently under study.



Scheme 2 Conversion of ester **7b** into 20(*S*)-camptothecin (**1**).

Acknowledgements

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16 (*a*) By HPLC: ChiralpakAD–H, 5 mm, isopropanol : hexane = 1 : 4, 0.5 mL min^{-1}. t_R of *R* isomer = 14.0 min; t_R of *S* isomer = 15.2 min. The *S* configuration was assigned by analogy[15a] and was subsequently confirmed through the synthesis of the natural product; (*b*) The reaction was run with 14% catalyst at −90 °C. At higher temperatures, there was significant secondary alcohol formation.

17 Natural camptothecin was recovered enantiopure[18] and in >80% yield after 5 h in refluxing 48% aqueous HBr.

18 By HPLC: Chiralpak AS, 5 mm, isopropanol : hexane = 1 : 1, 0.5 mL min^{-1}. t_R of *R* isomer = 41.5 min; t_R of *S* isomer = 34.6 min.

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23 The authentic sample of 20(*S*)-camptothecin was purchased from Sigma-Aldrich ($[\alpha]^{20}_D$ +43 (*c* 0.2 in 1 : 4 MeOH : $CHCl_3$), mp 260–261 °C, dec.).