Cascade Radical Reactions of Isonitriles: A Second-Generation Synthesis of (20*S*)-Camptothecin, Topotecan, Irinotecan, and GI-147211C**

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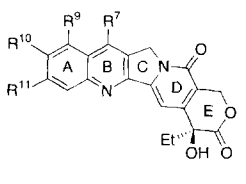
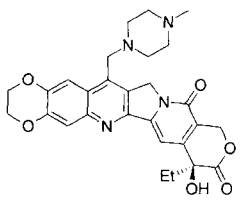
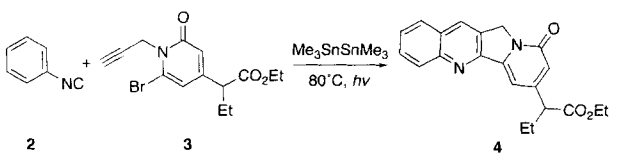
The camptothecin family of molecules has recently moved to the forefront of research in the treatment of solid tumors by chemotherapy.[1] The parent of this family, (20*S*)-camptothecin (**1a**), is highly active, and it is thought to operate by interfering with the unwinding of DNA by the enzyme topoisomerase I.[2] Camptothecin's clinical use has been limited by its insolubility, but extensive structure–activity studies have identified many analogs of camptothecin with equal or better antitumor activity and with better solubility properties.[3] Generally speaking, substitution at C7 and C9–C11 is permitted, while substitution at other positions tends to decrease or completely eliminate activity. Several analogs of camptothecin with improved solubility in water, including topotecan (**1b**),[1] irinotecan (**1c**),[1] and GI-147211C (**1d**),[4] are now in various stages of clinical trials around the world.





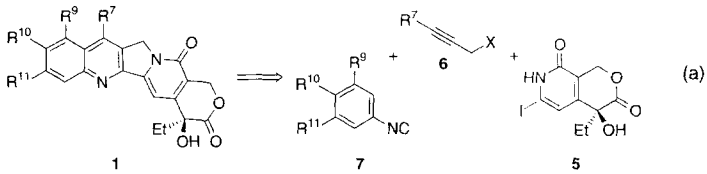
1a, camptothecin, R^7-R^{11} = H
1b, topotecan, R^7,R^{11} = H, R^9 = CH_2NMe_2, R^{10} = OH
1c, irinotecan, R^7 = Et, R^9,R^{11} = H, R^{10} = OCON
1d, GI-147211C

The synthesis of camptothecin was an active area of research about 20 years ago,[5] and the medicinal importance of this family has now rekindled interest. A number of new syntheses and significant improvements to existing syntheses have recently been reported.[6] In late 1992, we described a formal synthesis of racemic camptothecin that featured a new radical cascade reaction.[7] Reaction of phenyl isonitrile (**2**) with the readily available bromopyridone **3** provided the well-known "Danishefsky tetracycle" **4**.[8] Though very short (8 steps) and efficient, this synthesis suffered from two major problems: 1) the final products were racemic; and 2) the introduction of the E-ring lactone by hydroxymethylation of **4** occurred in poor yield, and the conditions were not tolerant of substituents on the A and B rings.[7d]



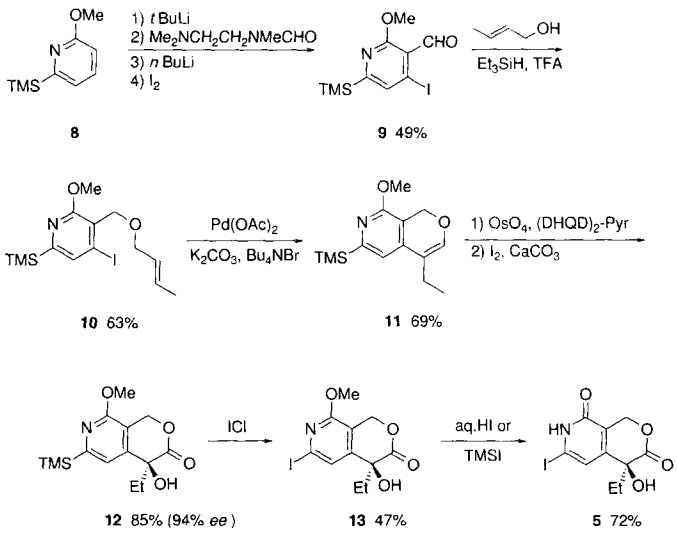
2 **3** **4**

Because the cascade radical reaction should tolerate all kinds of A- and B-ring substituents, we reformulated the synthetic plan to proceed via the key pyridone lactone **5** [Eq. (a)]. Variation of the propargyl substituent R^7 in **6** (X = I, Br) and the aryl substituents of isonitrile **7** should then allow access to camptothecin as well as known and new analogs. We now report a highly convergent second-generation synthesis of (20*S*)-camptothecin (**1a**). The synthesis is well suited to preparing A- and B-ring analogs of camptothecin, and to demonstrate this we have also synthesized GI-147211C (**1d**) and the immediate precursors of topotecan (**1b**) and irinotecan (**1c**).



1 **7** **5** (a)

The synthesis of lactone **5** is summarized in Scheme 1. Metalation of 2-bromo-6-methoxypyridine and quenching with TMSCl provided **8**. This was then converted in one step to iodoaldehyde **9** by following the procedure of Comins.[9] The E ring was then introduced by a sequence of reductive etherification[10] to form **10** and subsequent Heck reaction[11] to give enol ether **11**.[12] The Sharpless asymmetric dihydroxylation[13] of **11** followed from a model study,[14] and **12** was obtained in 85% yield and 94% *ee* after oxidation of the intermediate α-hydroxy lactol.[12] Exchange of the TMS group in **12** for iodine occurred upon exposure to ICl.[5] At about 50% conversion of **12** the reaction rate slowed dramatically. When the reaction was stopped at this point, iodide **13** was isolated in 47% yield and **12** was recovered in 45% yield. Demethylation of **13** then provided **5**.



8 **9** 49% **10** 63% **11** 69% **12** 85% (94% *ee*) **13** 47% **5** 72%

Scheme 1. Synthesis of intermediate **5**. TMS = trimethylsilyl, TFA = trifluoroacetic acid.

N-Propargylation of **5** under optimized conditions[16] with **14a** provided **15a** in 88% yield. In the key radical cascade,[17] a solution of **15a**, phenyl isonitrile (**2**), and hexamethyldistannane (1.5 equiv) in benzene was warmed to 70 °C and irradiated with

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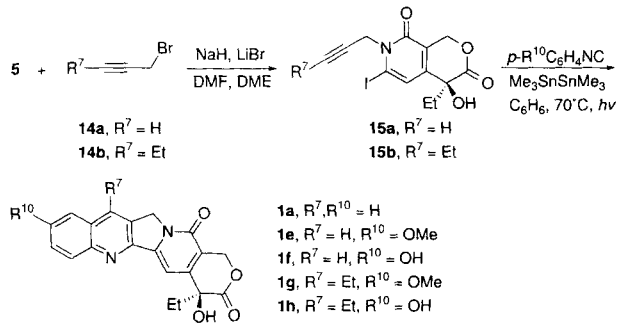
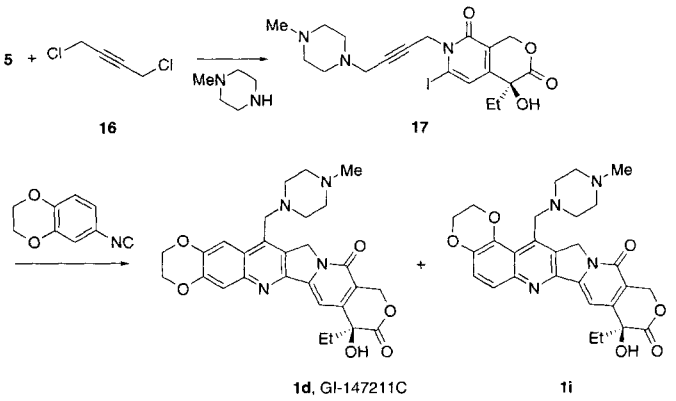


a sunlamp. Highly enantiomerically enriched (20*S*)-camptothecin (95% *ee*) crystallized from the reaction mixture and was isolated in 63% yield by simple filtration and washing with ether. Camptothecin (**1a**) could also be produced by substituting hexamethyldisilane for the distannane (52%) or by using *t*-butyl alcohol as the solvent (45%). Reaction of **15a** with *p*-methoxyphenylisonitrile provided **1e** in 51% yield, and subsequent demethylation with HBr provided 10-hydroxycamptothecin (**1f**).[18] This highly active natural product is the precursor of topotecan (**1b**).[19]

To prepare irinotecan (**1c**), lactone **5** was N-propargylated with **14b**, and the resulting product **15b** was treated with *p*-methoxyphenylisonitrile under the standard conditions. Demethylation of the product **1g** with HBr then gave 7-ethyl-10-hydroxycamptothecin (**1h**),[18] which is both a synthetic precursor of irinotecan (**1c**)[20] and the active antitumor agent produced in vivo when irinotecan is metabolized.[21]

The synthesis of GI-147211C (**1d**) starts with N-propargylation of **5** with **16** followed by addition of *N*-methylpiperazine to provide lactone **17**. Reaction of this lactone with 3,4-ethylenedioxyphenylisonitrile then provided an inseparable 3:2 mixture of GI-147211C (**1d**) and its regioisomer **1i** in 57% yield. This reaction illustrates a frequent regiochemical problem that occurs when *meta*-substituted isonitriles are used in radical cascade reactions.[17] A strategic solution to this problem has recently been developed and this will be reported separately.



This synthesis of camptothecin and its analogs provides a graphic demonstration of the power of cascade radical reactions. The approach is short and efficient, and it may be useful for preparing larger quantities of these compounds. Perhaps more importantly, the modular "mix-and-match" strategy [Eq. (a)] implemented in the radical cascade is ideally suited to the known structure–activity relationship of the camptothecin family. Lactone **5** is an invariant module that can be combined in as few as two steps with two variable modules—propargyl bromide **6** and aryl isonitrile **7**—to give a member of the camptothecin family. Because the radical reaction tolerates functional groups, the strategy promises to be useful in preparing a large assortment of both known and new analogs of camptothecin.

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