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Towards new anticancer drugs: a decade of advances in synthesis of camptothecins and related alkaloids

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Dedicated to Professor Dennis P. Curran on the occasion of his 50th birthday

Contents

1. Introduction

Camptothecin **1** (CPT) is a natural product that has been attracting a tremendous amount of attention and long lasting interest from both the academic community and the pharmaceutical industry. Isolated by Wani and Wall in 1966 from *Camptotheca acuminata* (Xi Su) that originated in China,[1,2] this alkaloid showed excellent antitumor activity, and thus became a prominent lead for anticancer drug development. Two of its analogs are being used in clinic for treatment of cancers and several other analogs are currently under clinical development

Keywords: camptothecin; homocamptothecin; mappicine; anticancer drug; total synthesis; semisynthesis.

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at various stages. One or more new anticancer drugs of this family are expected to emerge in the coming years. This review summarizes advances in synthesis of camptothecin, anticancer drug and drug candidates of this family and related alkaloids from early 90s to early 2003, which have been driving this exciting development of new anticancer drugs.

Camptothecin is a representative member of a family of natural products. Some members of this family are shown in Figure 1. They share the same highly conjugated polycyclic quinoline core (11*H*-indolizino[1,2-*b*]quinoline-9-one, Fig. 2), which contributes to their distinct blue fluorescence. The naturally occurring camptothecins have recently been reviewed.[3]

Camptothecin quickly entered clinical trials in the form of its water-soluble sodium salt in early 1970s. The highly conjugated aromatic structure and excellent antitumor activity stimulated synthetic studies on this natural product. During late 1960s and 1970s, interest in camptothecin was high and a number of total syntheses were accomplished. These 'first generation' syntheses were reviewed by Hutchinson in 1981.[4] However, the clinical trials of camptothecin sodium salt failed and the interest in camptothecin subsided for over a decade. The early development of camptothecin was reviewed.[4,5]

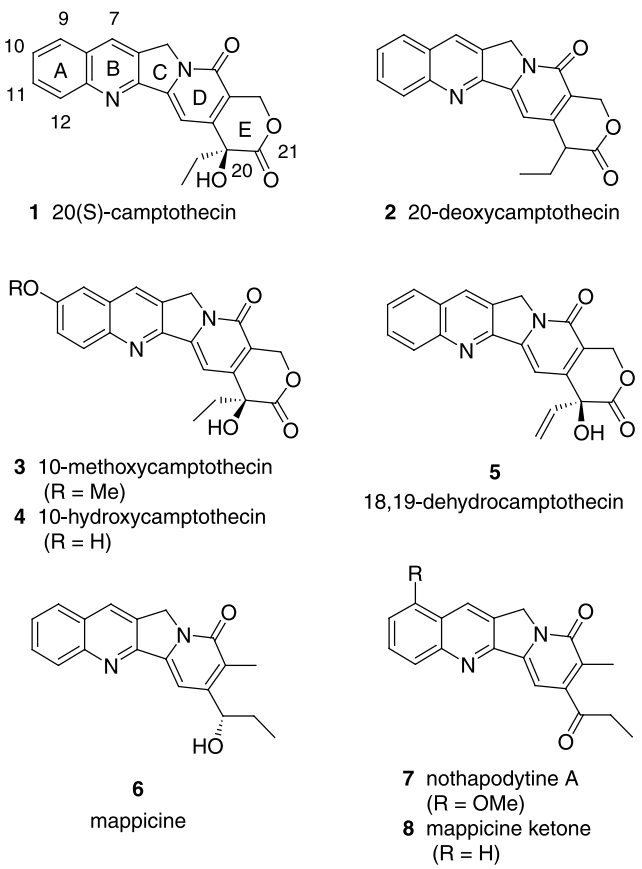


Figure 1. Some natural products of camptothecin family.

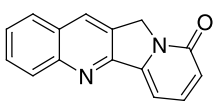


Figure 2. The aromatic core of camptothecins.

A histogram of publications on camptothecin reflects fluctuation of interest and research intensity in this field (Fig. 3). Between 1966 and 2002, there are over three thousand publications (journal articles and patents) on camptothecin. A dramatic increase of publications started from the late 1980s.

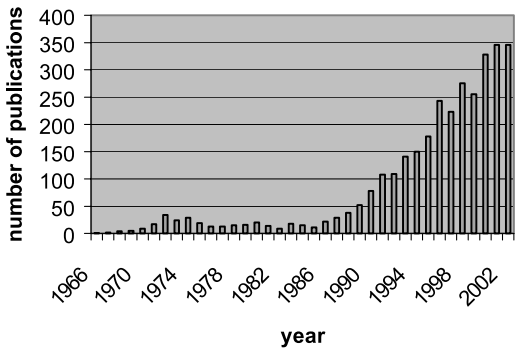


Figure 3. Histogram of publications on camptothecin (Scifinder, CAPLUS database).

The breakthrough that revived interest in camptothecin came from studies on its mechanism of action. In the late 1980s, it was discovered that camptothecin interacts with DNA topoisomerase I. Essential for DNA replication, topoisomerases are enzymes that catalyze the topoisomerization reactions (relaxation/supercoiling, knotting/unknotting and catenation/decatenation) of DNA.[6] For example, topoisomerase-I interacts with DNA double strand to form an enzyme-linked single-strand break and, after unwinding the supercoiled DNA, rejoins the single strand so that DNA replication can proceed. Camptothecin interferes with the religation by binding to the DNA–enzyme binary complex. This results in the accumulation of a reversible enzyme–camptothecin–DNA ternary complex (termed the cleavable complex), which is believed to cause cell death. A fork collision model has been proposed for camptothecin cytotoxicity.[7] The structure of the cleavable ternary complex is of great interest for elucidation of the mechanism of action and development of new topoisomerase inhibitors. Two binding models were proposed by Pommier[8] and Hol[9] with their co-workers in 1998. New insight of the mechanism of topoisomerase I poisoning by camptothecins was recently reported based on the X-ray crystal structure of the ternary complex.[10]

The discovery of topoisomerases as new targets for cancer chemotherapy and the mechanism of action of camptothecin put camptothecin back on the frontlines of anticancer drug development.[11] Camptothecin's total synthesis, mechanism of action, structure–activity relationship, analog synthesis as well as pharmacology, formulation, drug delivery, preclinic studies and clinic trials have been extensively

studied. The New York Academy of Science organized two international meetings devoted exclusively to camptothecin in 1996 and 2000.[12,13] As the result of these efforts, topotecan **9** (Fig. 4) was approved by the FDA for treatment of ovarian cancer and small-cell lung cancer[14] and irinotecan **10** for treatment of colorectal cancer.[15] Currently, topotecan is sold by Glaxo-SmithKline under the brand name 'hycamptin' (www.hycamptin.com). Irinotecan is sold by Pharmacia under the brand name 'camptosar' (www.camptosar.com).

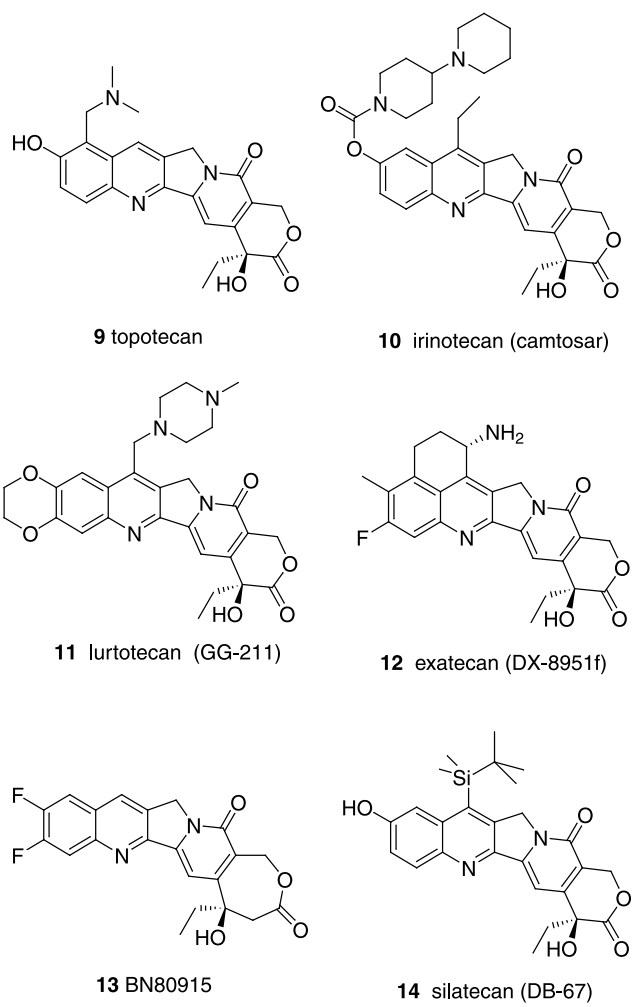


Figure 4. Anticancer drugs and some drug candidates for camptothecin family.

Besides continued studies on topotecan and irinotecan, much effort has also been spent on development of new anticancer drugs of this family. Figure 4 shows some important camptothecin analogs that entered or are poised to enter clinical trials as anticancer drug candidates. The pharmaceutical development of anticancer drug of camptothecin family has been addressed by several recent reviews in more detail.[16–20]

This review summarizes the advances on total synthesis of camptothecin and synthesis of important drug candidates since early 1990s. There are several reviews concerning synthesis of camptothecins.[21–24] However, they are more medicinal chemistry oriented, and with rapid developments in this field, a more comprehensive and up-to-date review is needed. Mappicine ketone **8** shows significant cytotoxicity in the human KB cell line[25] and has been identified as an antiviral lead against herpes viruses (HSV) and human cytomegalovirus (HCMV).[26,27] Thus both mappicine **6** and mappicine ketone **8** are also targets for synthetic chemists. Many methods for synthesis of camptothecin have been applied to synthesis of mappicine and mappicine ketone. Therefore, their syntheses are briefly addressed here. Included here are also some model studies on synthesis of camptothecin by using novel methodologies, while some modified synthetic routes[28,29] using previously reported strategy are not discussed in detail here. Besides total synthesis of camptothecin, much synthetic effort has been spent on preparing camptothecin analogs for structure–activity relationship studies. The medicinal chemistry of camptothecin is not the main topic of this review thus will only be briefly discussed when relevant.

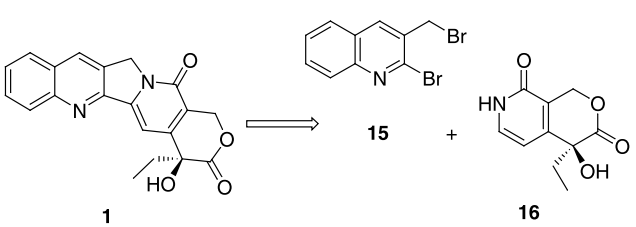
This review is organized according to synthetic strategies toward camptothecin skeletone. As shown in Figure 5, the major synthetic approaches are roughly classified as the C-ring construction approach, the cascade radical cyclization approach, the broadly applied Friedlander condensation approach, various Michael addition approaches, and various Diels–Alder reaction approaches. Each of these synthetic routes represents either a highly efficient and practical synthesis of camptothecin, a pioneering development of new synthetic methodology, or a unique synthetic approach.

2. The C-ring construction approach

Retrosynthetic disconnection of camptothecin at the C-ring is straightforward. This approach features a *N*-alkylation and a sp^2–sp^2 C–C bond formation as two key reactions. As represented by Comins's total synthesis, this approach provides a short and efficient route to the natural product.

2.1. Comins's total synthesis of (+)-camptothecin and (±)-mappicine

The Comins's group has reported several related total syntheses of camptothecin that were accomplished in a convergent manner through joining of the AB ring and the DE ring through construction of the C ring. Their first total synthesis in 1992 called for a bromoquinoline **15** as the AB ring fragment, and a lactone **16** as the DE ring fragment (Scheme 1).[30]



Scheme 1.

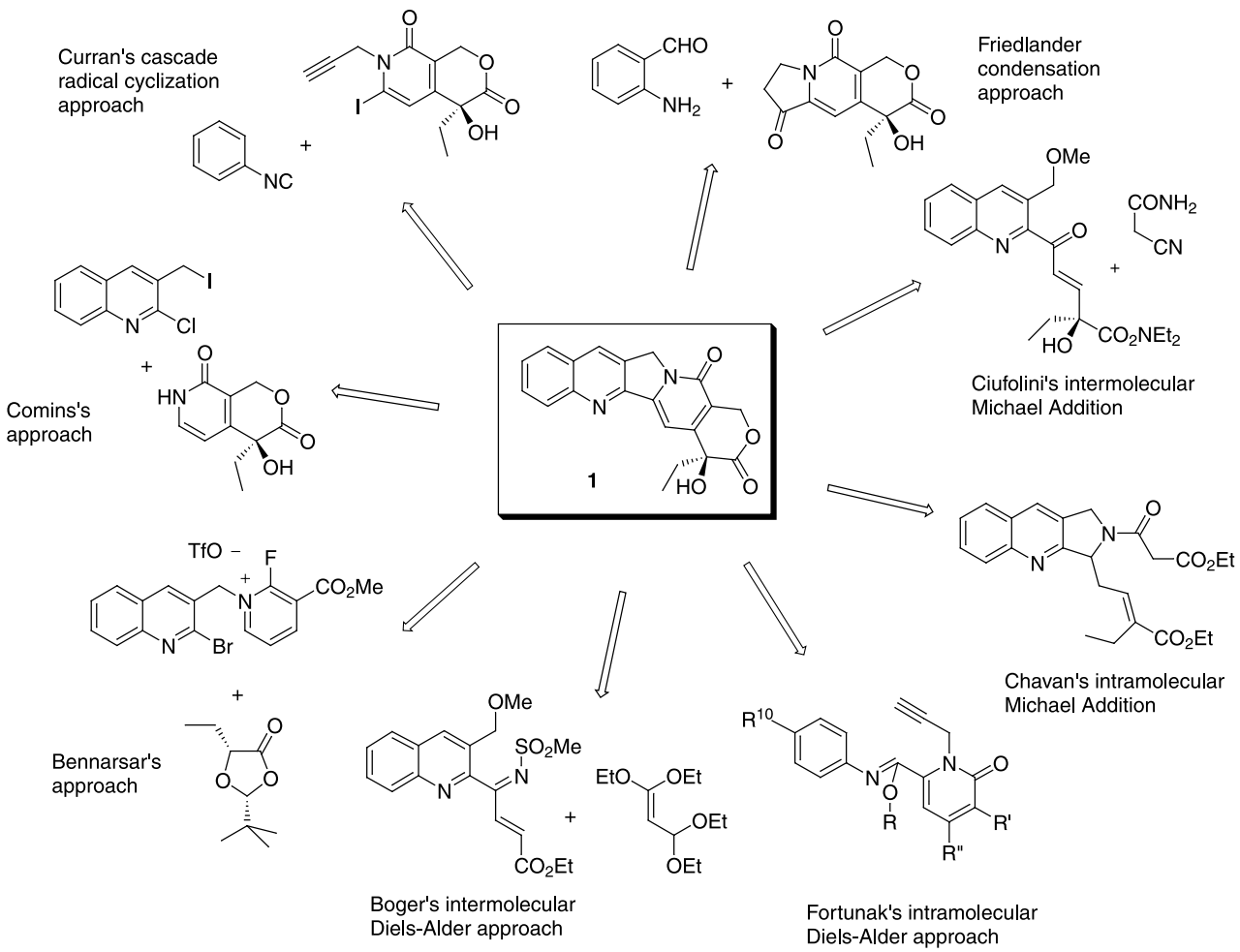


Figure 5. Total syntheses of camptothecin.

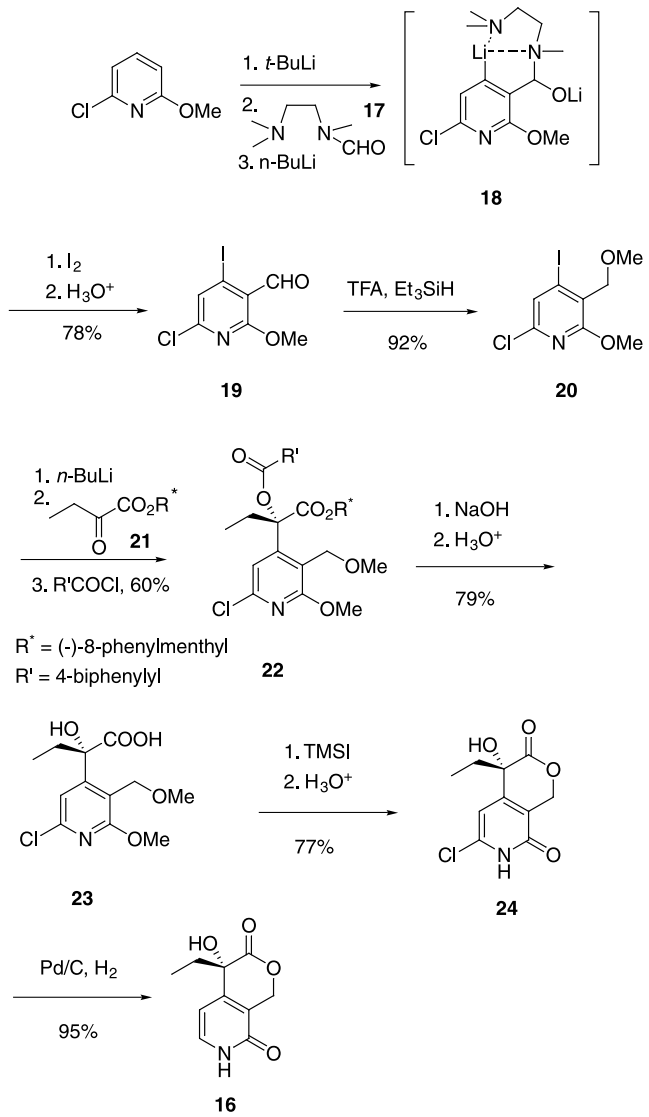
As shown in Scheme 2, the enantiomerically pure α-hydroxy lactone DE fragment **16** was prepared from commercially available 2-chloro-6-methoxy pyridine. Lithiation followed by trapping with formamide **17** gave intermediate **18**, which was subsequently quenched with I_2 to give aldehyde **19**. Reduction of this aldehyde with TFA and Et_3SiH in methanol gave ether **20**. The key tertiary alcohol was then synthesized by chiral auxiliary chemistry. Lithation of **20** followed by addition of α-keto ester **21** that has a menthyl chiral auxiliary and subsequent trapping the resulting alkoxide gave crude ester **22** with 87% de. The product was recrystallized to give diastereomerically pure **22** in 60% yield. The chiral auxiliary was removed by basic hydrolysis to give acid **23**. Deprotection of the methyl ether using TMSI generated in situ from TMSCl/NaI and subsequent treatment with aqueous acid yielded lactone **24**, which was then converted to lactone **16** by catalytic hydrogenolysis.

Completion of the total synthesis is shown in Scheme 3. Treatment of commercially available 2-chloroquinoline with LDA followed by formaldehyde gave quinoline **25**, which upon treatment of PBr_3 yielded bromoquinoline **15**. Alkylation of **16** gave *seco*-compound **26**. The final construction of the C-ring was accomplished by a Heck reaction to give **1** in 59% yield.

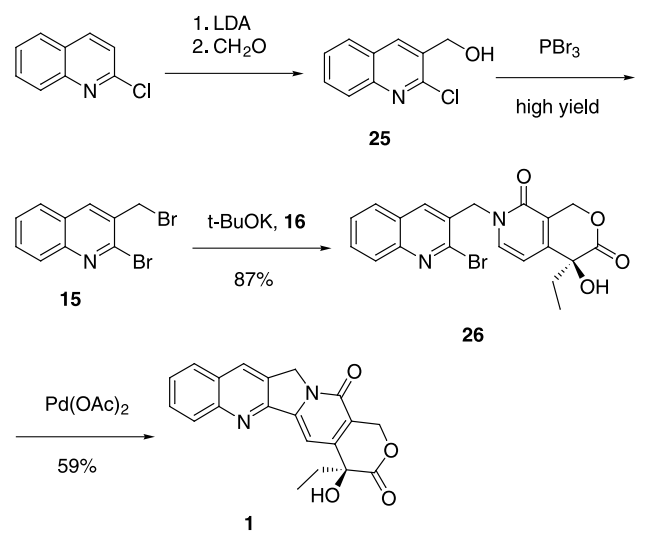
Since Comins's first report on this approach, several modifications were introduced to allow a shorter and more efficient synthesis of camptothecin. Two papers deal with the synthesis of the DE lactone **16**. One approach used methylene acetal as an efficient dual protective group for two hydroxy groups (Scheme 4).[31]

Protection of the hydroxy group in 2-chloro-6-hydroxy pyridine gave pyridine **27**. Then a one-pot procedure including lithiation, trapping by formamide **17**, second lithation, iodination and finally reduction using $NaBH_4$ gave alcohol **28** in 41% yield. Treatment of **28** with $BF_3{\cdot}OEt_2$ gave iodopyridine **29** in which both hydroxy groups were protected. Lithiation followed by addition to a chiral α-ketoester **30** gave alcohol **31** in 88% de. Further purification by radial plate liquid chromatography removed the minor diasteromer and yielded **31** in 63% yield. Treatment of **31** with 10% HCl gave **24** in 75% yield along with the recovered chiral auxiliary.

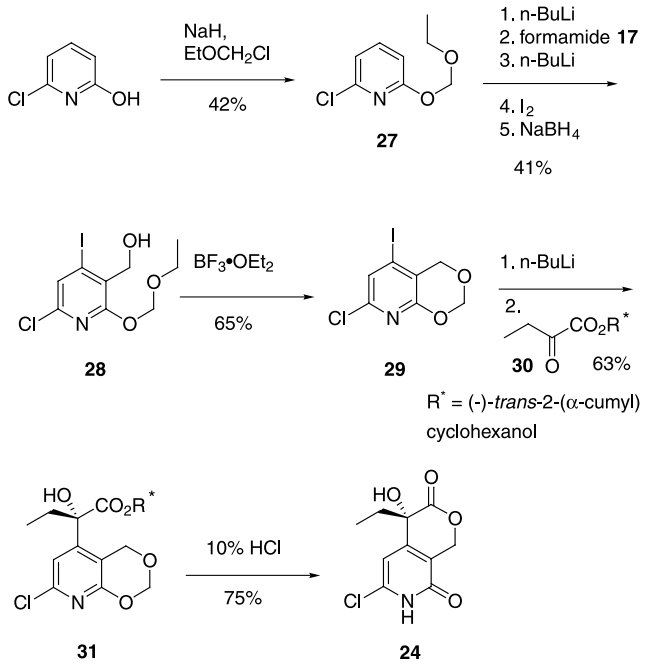
In another modification on synthesis of **16**, the addition to the α-ketoester was performed directly, instead of going through iodopyridine intermediate **29**.[32] As shown in Scheme 5, sequential treatment of 2-methoxypyridine with mesityllithium, formamide **17** and *n*-BuLi generated lithium intermediate **32**. This dianion was too basic to add to enolizable methyl α-ketobutyrate, so its basicity was reduced by metal exchange with $CeCl_3$. Subsequent



Scheme 2.



Scheme 3.

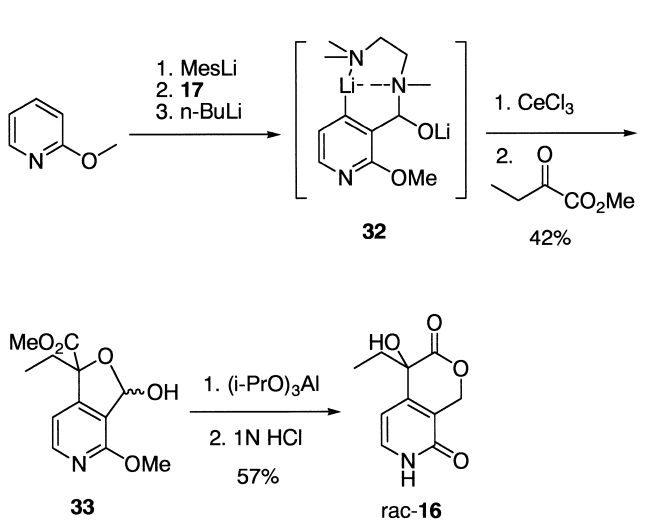


Scheme 4.

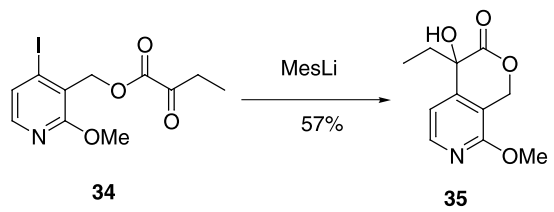
addition to methyl α-ketobutyrate resulted in lactol **33** as a mixture of diastereomers. Reduction using aluminum reagent followed by deprotection of the methyl ether gave racemic **16** in 57% yield.

The addition to an α-ketoester can also be done intramolecularly. Mesityllithium was found to be an excellent chemoselective lithiation reagent to generate aryllithium even in the presence of alkoxycarbonyl group.[33] Treatment of ketoester **34** with mesityllithium at −78°C for 1 h gave racemic lactone **35** in 57% yield (Scheme 6).

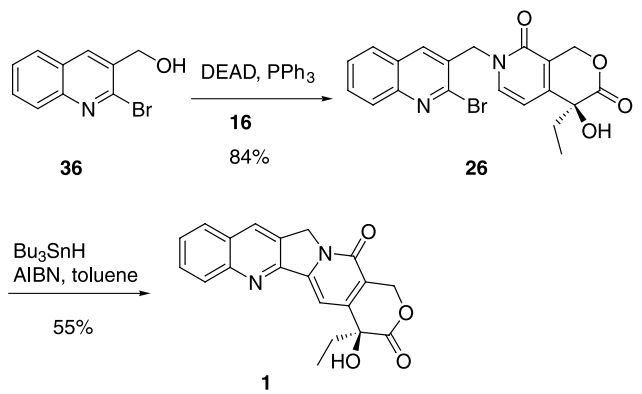
Alternative conditions for construction of the C-ring were also studied (Scheme 7). The Mitsunobu conditions were applied on *N*-alkylation, and a radical cyclization was developed to replace the Heck reaction.[31] Treatment of **16** with alcohol **36**, DEAD and PPh_3 yielded **26** in 84% yield.



Scheme 5.



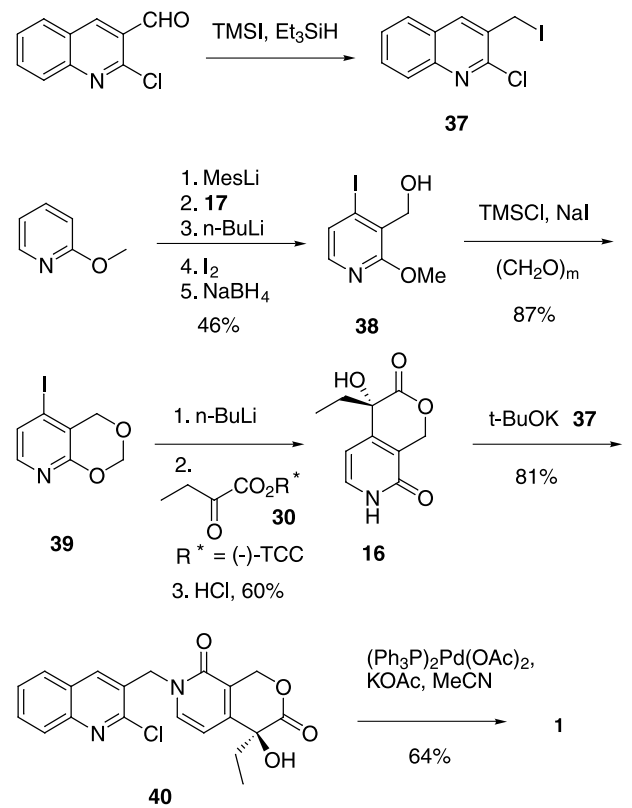
Scheme 6.



Scheme 7.

The radical cyclization of **26** with tributyltin hydride/AIBN conditions gave **1** in 55% yield.

Recently, the Comins group claimed the shortest asymmetric synthesis of camptothecin though a six-step sequence (Scheme 8).[34] Some of previously reported reactions were conducted in one-pot. A better alkylation reagent quinoline



Scheme 8.

37 was prepared from commercially available 2-chloro-3-formyl quinoline by treatment of TMSI and triethylsilane. Pyridine **38** was prepared from 2-methoxy pyridine using reported procedures. Deprotection of the methyl ether in **38** and dual protection of the two hydroxy groups were accomplished in one pot under TMSI/paraformaldehyde conditions to give **39**. Lithiation of **39**, addition to keto ester **30**, subsequent deprotection and simultaneous lactonization were accomplished in one pot to give lactone **16** in 60% yield and 93% ee after recrystallization. Following the original protocol, alkylation of **16** with **37** gave **40**, which was then subjected to Heck conditions to give camptothecin **1** in 64% yield.

The same approach was also used by the Comins group to synthesize mappicine ketone and (±)-mappicine (Scheme 9).[35] Treatment of 2-fluoro-3-iodopyridine with LDA and MeI yielded iodopyridine **41**. This was treated with BuLi and propanal to give alcohol **42**, which was then converted to pyridone **43**. Alkylation of **43** with dibromide **15** gave *seco* compound **44**. Subsequent Heck reaction yielded mappicine ketone **8**, which upon $NaBH_4$ reduction gave (±)-mappicine **6**.

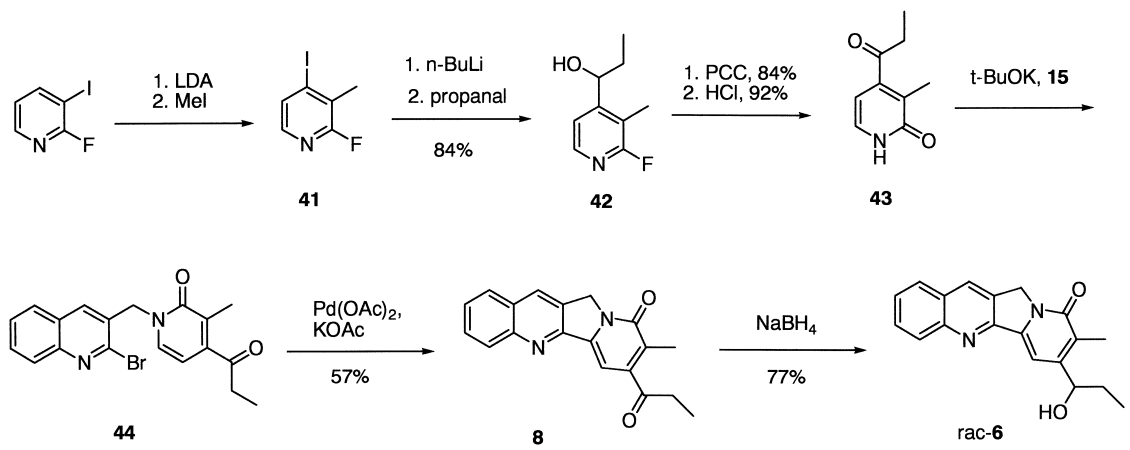
2.2. Glaxo Wellcome's total synthesis of lurtotecan

Lurtotecan is a camptothecin analog that was under development in Glaxo Wellcome, and has entered clinical trials by Glaxo. This drug candidate was first prepared using the Friedlander condensation approach that will be discussed later. A more practical total synthesis of this drug candidate was developed based on Comins's approach.[36]

Fang and co-workers in Glaxo developed a more practical asymmetric synthesis of the key intermediate **16** applying Sharpless asymmetric dihydroxylation reaction,[37] thus avoiding the use of stoichiometric amount of chiral auxiliary. As shown in Scheme 10, pyridine **45** was prepared from 2-methoxypyridine by using a procedure similar to that for **19**. Reductive etherification under TFA/Et_3SiH conditions gave ether **46**, which then underwent a Heck reaction to give cyclic vinyl ether **47** in 79% yield. Sharpless asymmetric dihydroxylation of **47** using $(DHQD)_2$–PYR ligand and $K_2OsO_2(OH)_4$ yielded the *cis*-diol **48**, which was then oxidized under $I_2/CaCO_3$ conditions to give lactone **35** with 94% ee. Deprotection of the methoxy group yielded pyridone **16** in 74% yield.

The preparation of the AB ring fragment of lurtotecan is shown in Scheme 11. Aniline **49** underwent a Friedel–Craft acylation with chloroacetonitrile mediated by BCl_3 or $AlCl_3$ to give a α-chloroketone **50**. Acylation and subsequent aldol condensation on ketone **50** yielded quinolone **51** in about 80% yield. Treatment of **51** with phosphorous oxyhalides provided high yield of **52** in which Y can be chloride and bromide. Reactions of **52** with *N*-methylpiperazine yielded amines **53**, which was reduced with DIBAL-H to give alcohols **54** in high yields.

The joining of AB ring fragment and DE ring fragment is shown in Scheme 12. Chloride **55** was not suitable for preparation of **57** because it is not stable. Upon standing, **55** was converted to quaternary ammonium salt **56**, which did



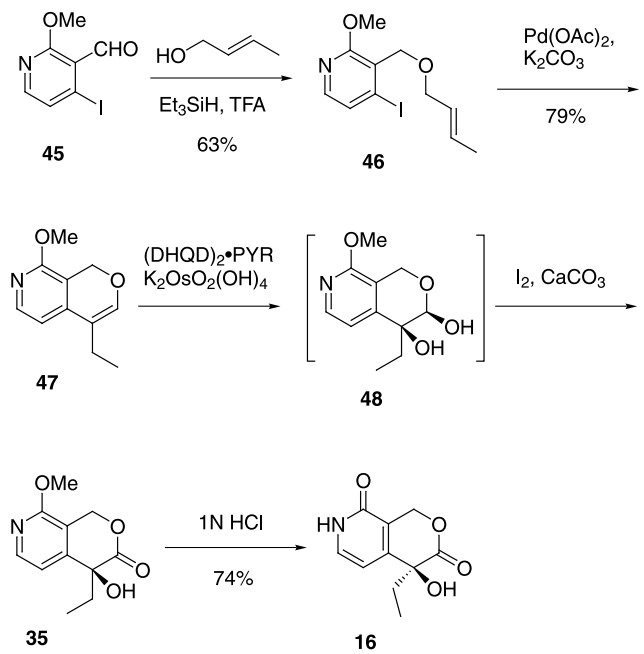
Scheme 9.

not condense with **16**. However, a Mitsunobu reaction successfully joined the two fragments together to give **57**. The yield varied from 34–71% with the different halides. Heck reaction under $Pd(OAc)_2$, Ph_3P conditions yielded the free base of lurtotecan **11**. Bromide **57b** and iodide **57c** gave a comparable 78 and 72% yield for this reaction. The free base was then treated with 6N HCl to generate the water-soluble ammonium salt of lurtotecan.

2.3. Homocamptothecins

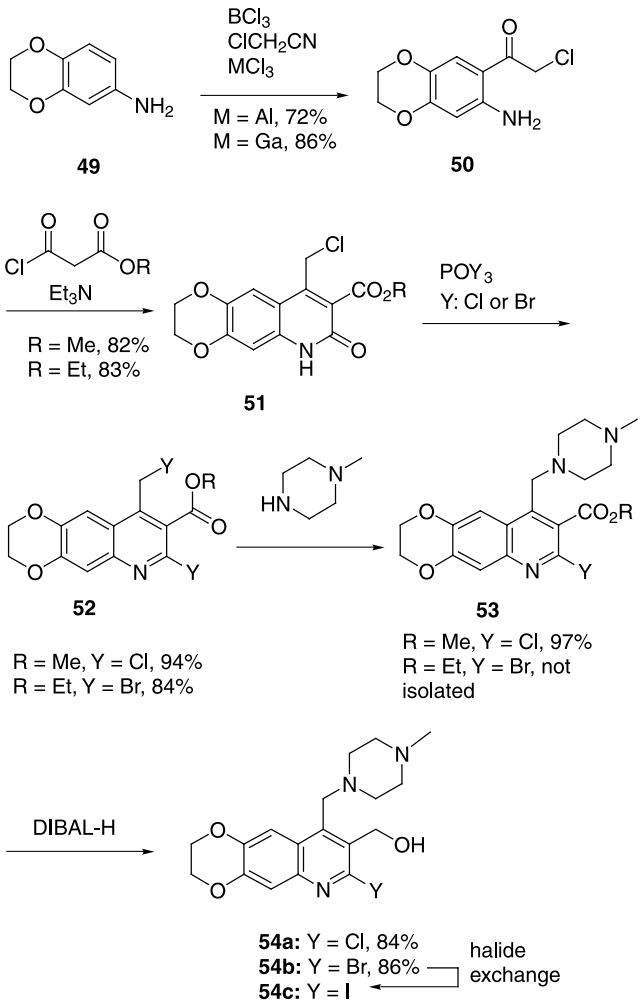
Camptothecins are known to hydrolyze in blood to give the inactive carboxylate.[38] Thus increasing the blood stability of camptothecin analogs is one of the most important goals in the development of new anticancer drugs of this family.

Bigg and co-workers found that homologation of the six-membered α-hydroxy lactone E-ring of camptothecin to a seven-membered β-hydroxy lactone (so called homocamptothecin) increased the E-ring stability while still maintaining antitumor activity and topo I inhibition activity. The discovery of homocamptothecin (hCPT, Fig. 6) opened new directions for camptothecin synthesis and its medicinal chemistry.

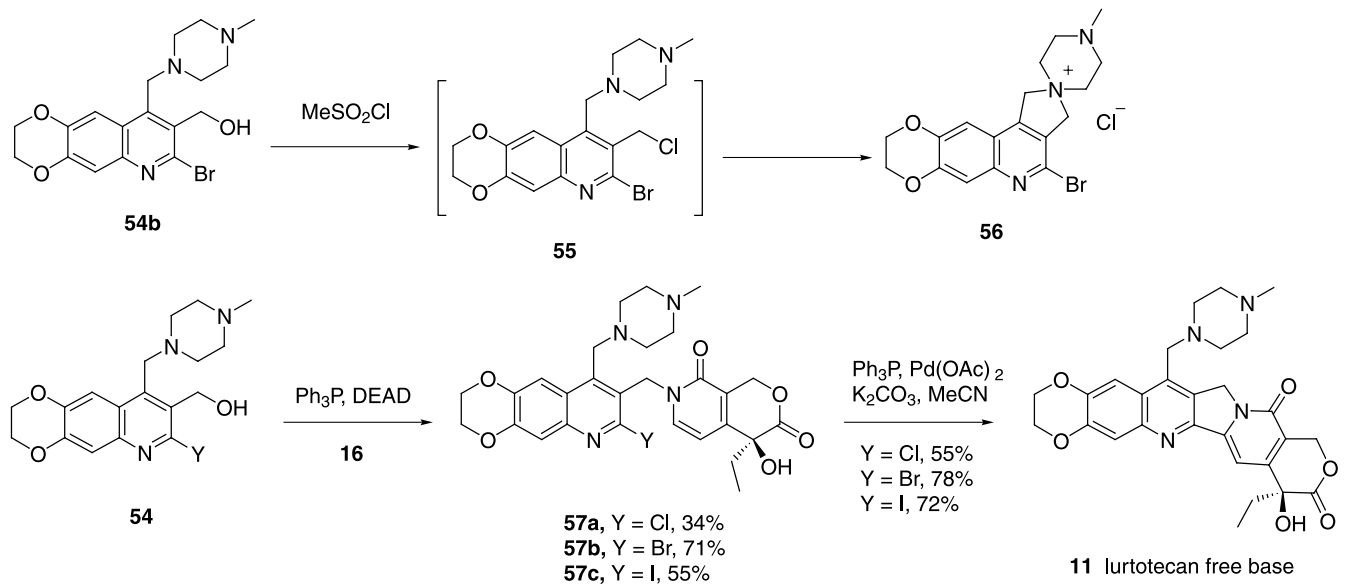


Scheme 10.

Homocamptothecin was first prepared in racemic form by a semi-synthesis.[39] Soon after that, a total synthesis was targeted for homocamptothecins to explore this new class of analogs.[40–43] The synthesis by Bigg, Lavergne and co-workers resembles the Comins route to camptothecin and is



Scheme 11.



Scheme 12.

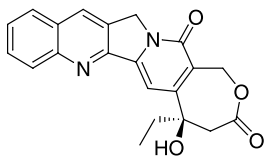
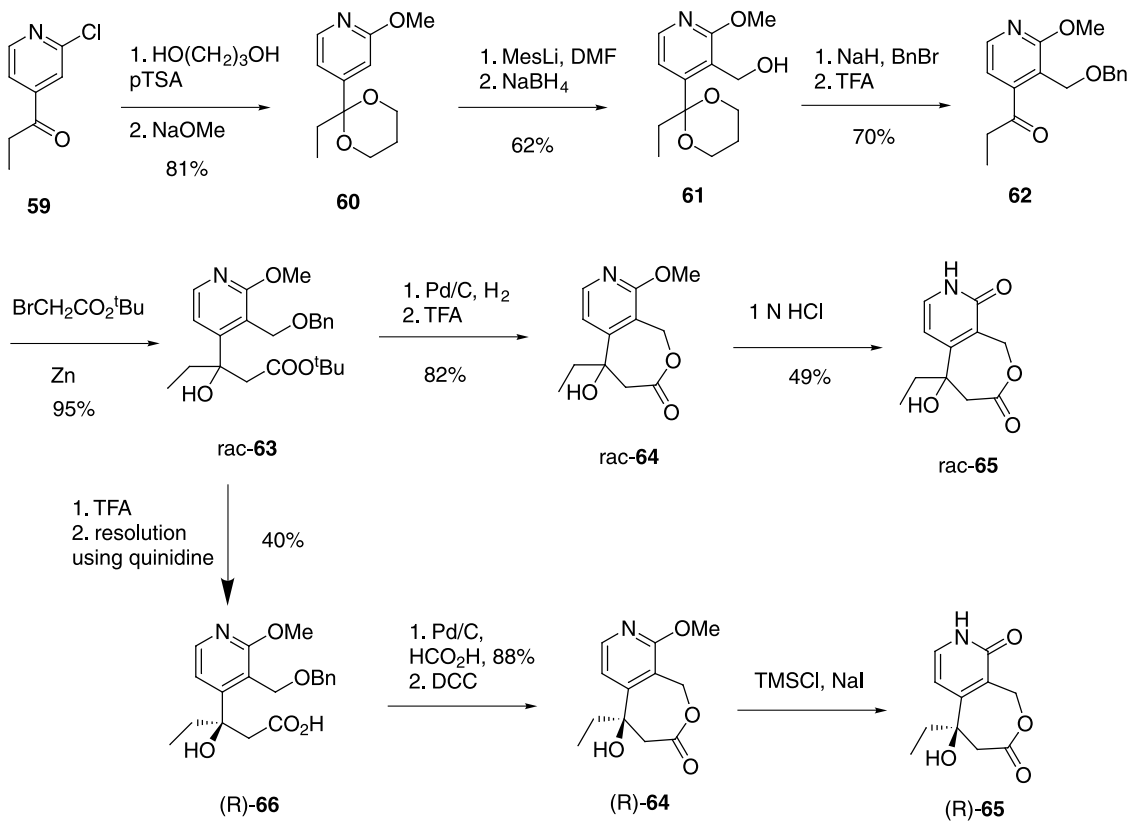


Figure 6.

shown in Scheme 13. The homologated Comins DE lactone **65** was first synthesized. Ketone **59** was converted to **62** in 3 steps. Reformatsky reaction was performed on ketone **62** to yield a β-hydroxy ester **63**. The benzyl ether in **63** was then removed under catalytic hydrogenolysis conditions and subsequent treatment with TFA gave lactone **64**. Final deprotection of the methyl ether gave the homologated DE lactone **65** in racemic form.



Scheme 13.

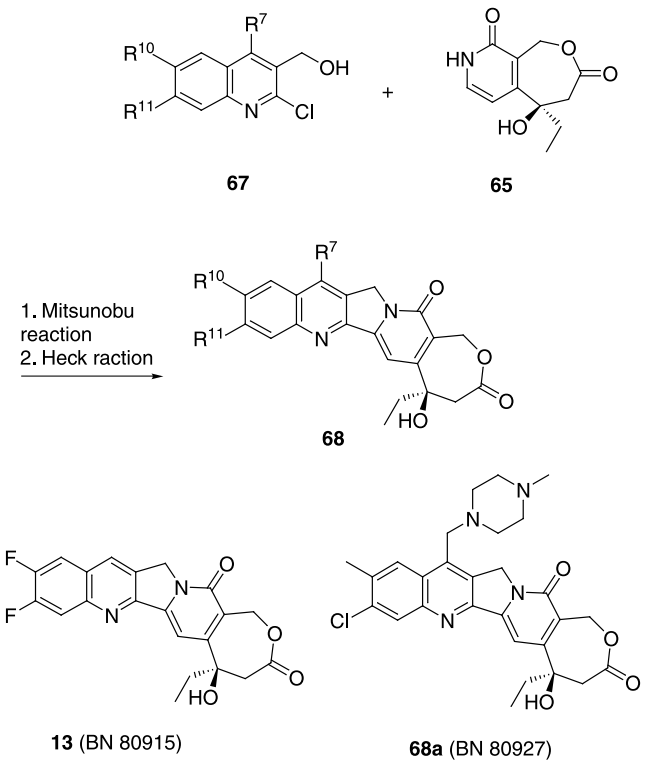


Figure 7. Homocamptothecin drug candidates.

Racemic **65** was used in synthesizing several homocamptothecin analogs. However, because of that enantiomerically pure **65** was needed to develop homocamptothecin type anticancer drug, a resolution procedure was then developed to provide (*R*)-**65**. Treatment of (±)-**63** with TFA removed the *t*-butyl ester to give a free acid. Subsequent treatment with quinidine in isopropanol gave a salt as a mixture of two diastereomers. The quinidine salt of (*R*)-**66** precipitated upon cooling, and was thus separated from its diastereomer. This resolution method provided (*R*)-**65** in 70% ee. It could be further purified by recrystalization. The *R* configuration was confirmed by X-ray diffraction on quinidium salt of (*R*)-**66**.

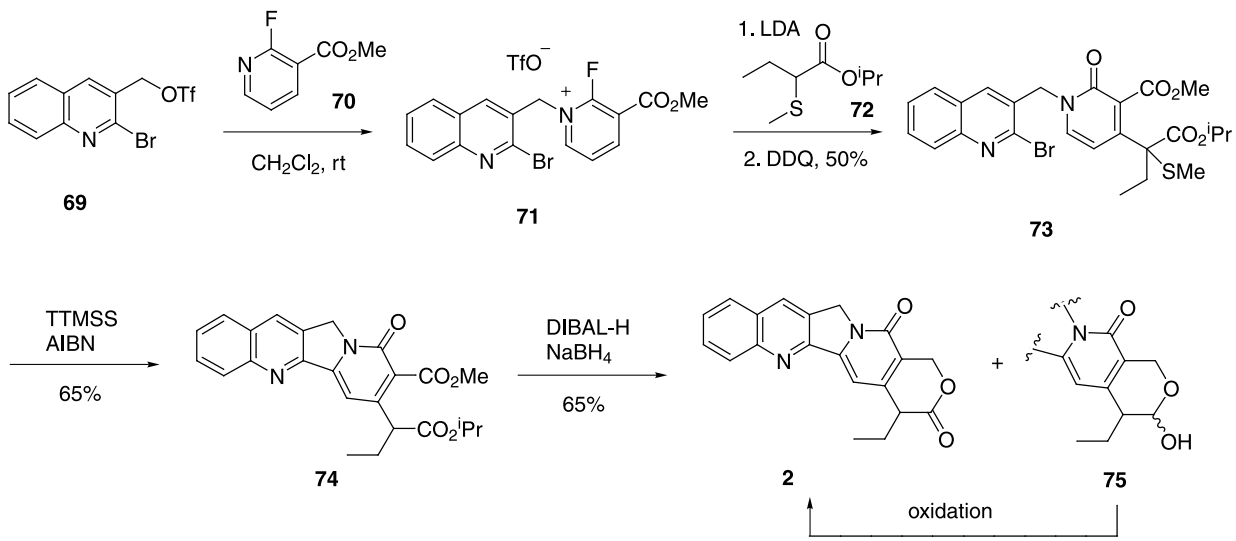
Various homocamptothecin analogs were synthesized by the Bigg group using the Comins approach (Fig. 7). The AB fragments **67** with various substituents were prepared by similar procedure described above. Joining **67** and **65** applying the Mitsunobu reaction and Heck reaction sequence yielded homocamptothecins **68**. Analogs **13** (BN 80915)[43] and **68a** (BN 80927)[41] were chosen as drug candidates for further clinical development.

2.4. Bennasar's total synthesis of (+)-camptothecin

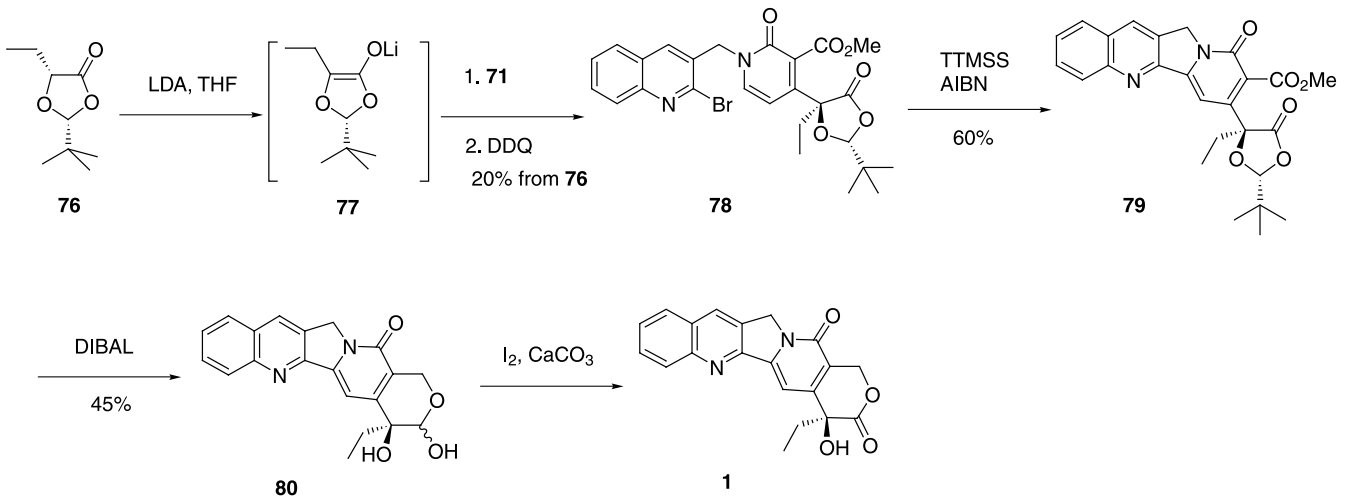
Bennasar's approach to camptothecin features enolate addition to a pyridinium salt that was formed during construction of the C ring. This approach demonstrated a well-designed reaction sequence that build CDE ring in a highly smooth way. A formal total synthesis of racemic camptothecin was first reported by the Bennasar group.[44] Then an asymmetric total synthesis of camptothecin was accomplished by using a chiral enolate.[45]

Bennarsar's formal synthesis is shown in Scheme 14. Mixing triflate **69** with fluoropyridine **70** resulted in pyridinium salt **71**, which was treated with an enolate prepared by reaction of ester **72** and LDA. The thiol ether substituent in **72** helps to improve the regioselectivity in the enolate addition. The addition product underwent DDQ oxidation and hydrolysis to give pyridone **73**, which upon treatment with TTMSS and AIBN yielded ester **74**. The two esters in **74** can be differentiated due to steric effects. Ester **74** was reduced with DIBAL-H and $NaBH_4$ to give a 1:1 mixture of lactone **2** and lactol **75**. The latter can be readily converted to **2** by oxidation. 20-Deoxycamptothecin **2** is a natural product and its conversion to racemic camptothecin is known.

The asymmetric synthesis of 20(*S*)-camptothecin was accomplished by addition of a chiral enolate to pyridinium salt **71** (Scheme 15). The enolate addition of **76** is a typical example of the concept 'self-reproduction of chirality'.[46] Addition of **77** to pyridinium salt **71** followed by DDQ oxidation and hydrolysis gave **78** in 20% yield. Radical cyclization of **78** furnished the C ring to give ester **79** in 60% yield. Treatment of **79** with DIBAL-H yielded lactol



Scheme 14.



Scheme 15.

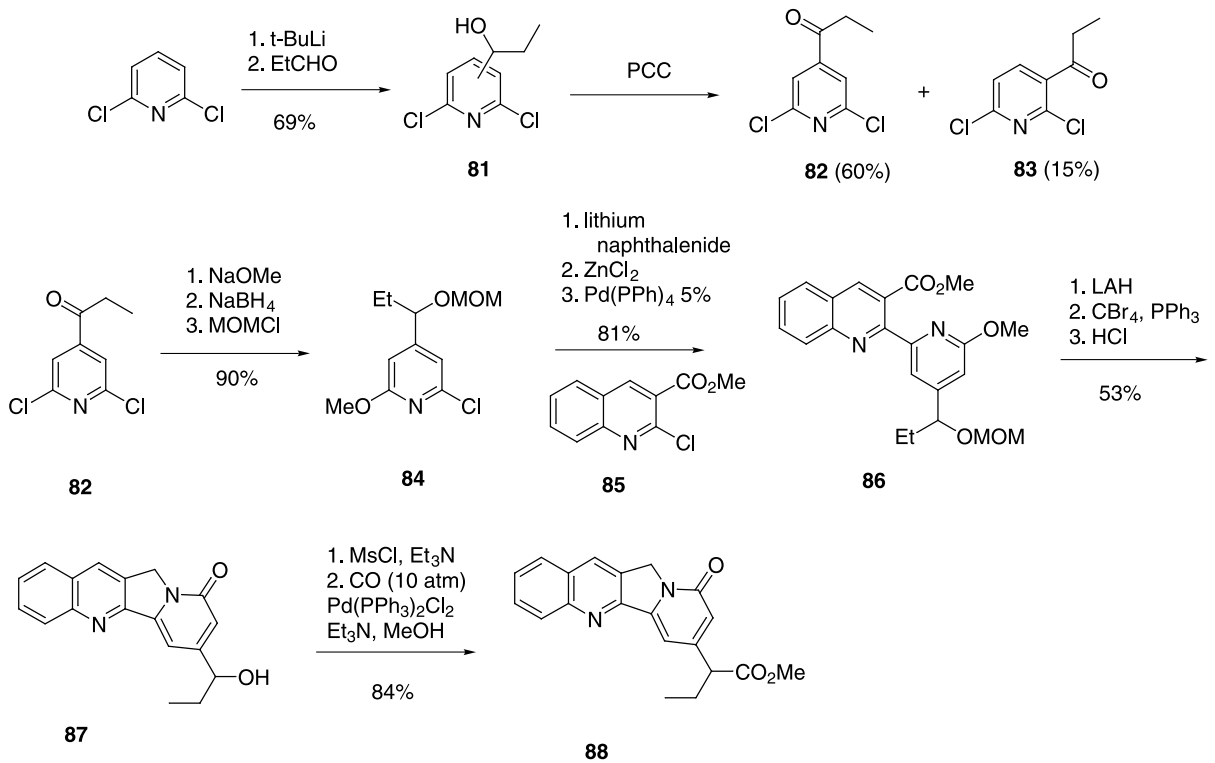
80, which was oxidized under $CaCO_3/I_2$ conditions to give 20(*S*)-camptothecin **1**.

2.5. Murata's formal total synthesis of (±)-camptothecin

Metallation is a powerful method for funtionalization of heteroaromatics. This is the theme demonstrated in a formal total synthesis of camptothecin reported by the Murata group (Scheme 16).[47] Lithiation of 2,6-dichloropyridine followed by quenching with propanal gave alcohols **81** as a mixture of regioisomers. After oxidation to ketones **82** and **83**, the regioisomers were easily separated. Ketone **82** was converted to methyl ether **84**, which upon lithiation, transmetallation and Pd-catalyzed Negishi coupling with chloroquinoline **83** yielded intermediate **86**. C ring construction was completed by subsequent reduction, bromide formation, deprotection and cyclization gave alcohol **87**. Palladium-catalyzed CO insertion followed by ester formation gave **88**, whose conversion to racemic camptotehcin is known.[4]

3. Cascade radical cyclization approach (B, C rings construction)

Curran's elegant syntheses of camptothecins and mappicines are the representatives of cascade radical cyclization approach. In the early 1990s, the Curran group initiated a research program aimed at developing new radical reactions of isonitriles. The isonitrile group has been recognized as a

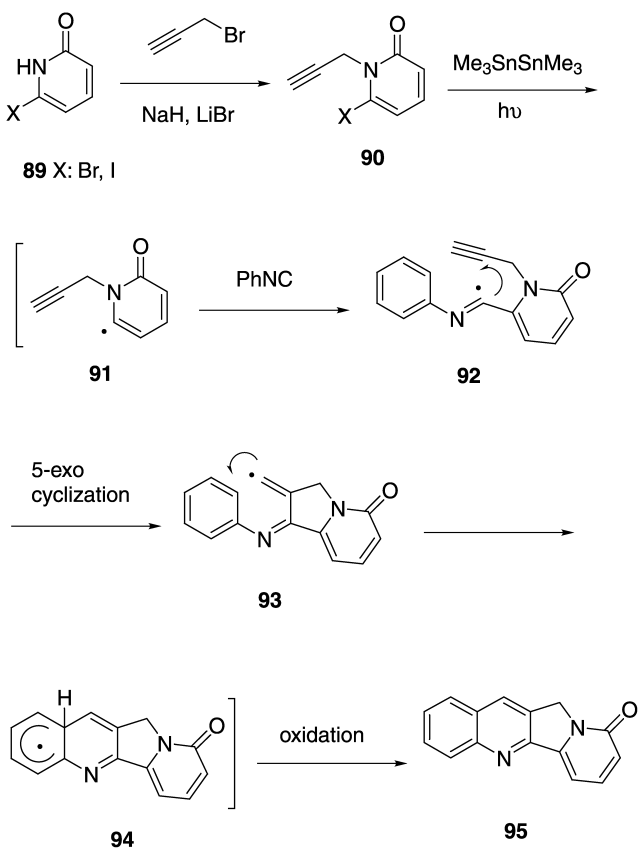


Scheme 16.

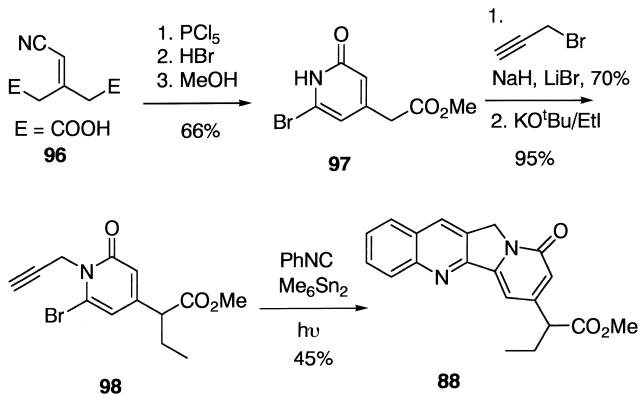
synthon of geminal radical precursor and acceptor in radical chemistry.[48,49] This research program resulted the discovery of the 4+1 radical annulation reaction of isonitriles that was used to synthesize cyclopenta-fused quinolines.[50] This cascade radical reaction was soon applied to formal total synthesis of racemic camptothecin and later asymmetric synthesis of camptothecin, mappicine and their analogs. In over ten years, the camptothecin and mappicine project in Curran group has evolved from a synthetic methodology research to a medicinal chemistry and drug discovery program. More recently, the 4+1 radical annulation reaction has been used in combinatorial chemistry and newly developed fluorous chemistry. Some of this work was briefly reviewed by Professor Curran.[51,52]

3.1. Curran's total synthesis of (+)-camptothecin and (−)-mappicine

The synthesis of a camptothecin model and suggested mechanism of this 4+1 radical annulation are shown in Scheme 17. Bromopyridone or iodopyridone **89** was propargylated under NaH/LiBr conditions to give halopyridone **90**. The optimum conditions for subsequent radical annulation were found to be irradiation using a sunlamp in the presence of a stochiometric amount of hexamethylditin. Under such conditions, hexamethylditin is homolytically cleaved to give the trimethyltin radical, which abstracts the halide from **90** to generate aryl radical **91**. Or alternatively, the C−X bond in **90** is cleaved under photolysis to give radical **91** and an iodine atom, which is then quenched by hexamethylditin. Radical **91** then adds to phenyl isonitrile to



Scheme 17.



Scheme 18.

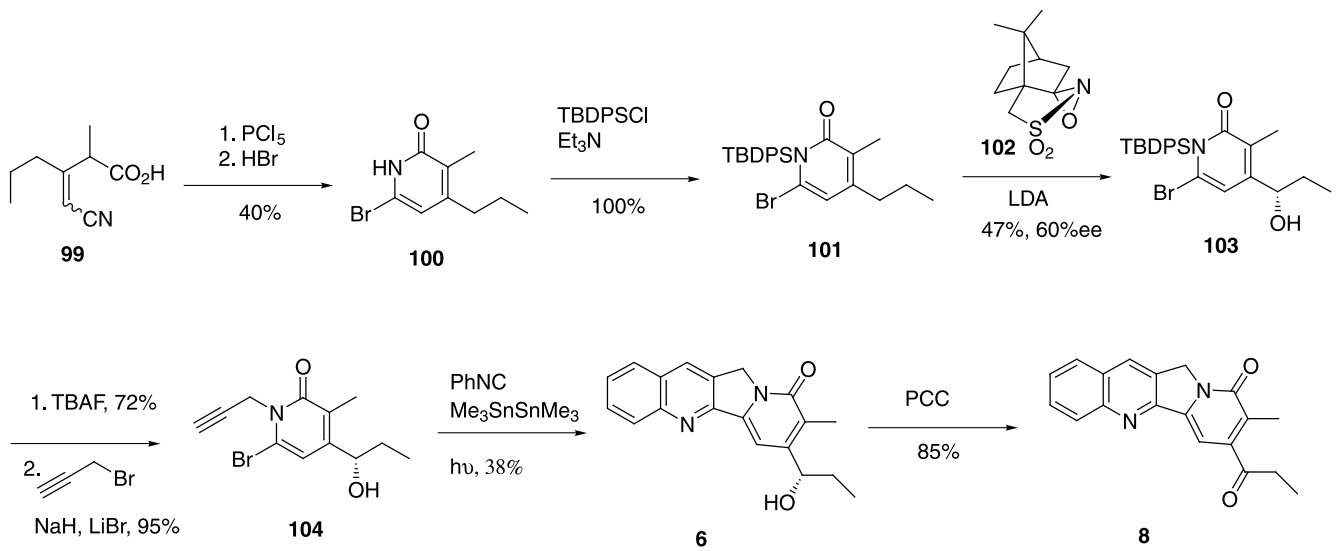
give imidoyl radical **92** which undergoes a 5-*exo* radical cyclization to give a vinyl radical **93**. Radical addition to the phenyl ring followed by oxidation generates quinoline **95**, which is the aromatic core of camptothecin.

Curran and Liu's first generation total synthesis of racemic camptothecin[53] is shown in Scheme 18. Diacid **96** was first treated with PCl_5 and then gaseous HBr. Addition of MeOH and workup gave bromopyridone **97**. *N*-Propargylation of **97** followed by α-ethylation of the ester yielded pyridone **98**. This compound was subjected to the photo irradiation conditions giving quinoline **88** in 45% isolated yield. Subsequent conversion of quinoline **88** to racemic camptothecin is known.[4]

This cascade radical annulation approach was also applied to asymmetric total synthesis of (*S*)-mappicine and mappicine ketone (Scheme 19).[54] Under similar conditions described in Scheme 18, acid **99** was converted to bromopyridone **100**. The pyridone nitrogen in **100** was protected with TBDPS group and subsequent asymmetric hydroxylation using Davis *N*-sulfonyl oxaziridine **102** yielded pyridone **103** in 47% yield and 60% ee. Compound **103** was then deprotected and propargylated to give pyridine **104**, which was subjected to radical annulation conditions to give (*S*)-mappicine **6** in 38% yield. Subsequent oxidation of **6** using PCC gave mappicine ketone **8**.

Although the synthetic potential of the 4+1 radical annulation was demonstrated in above formal total synthesis of camptothecin, the synthetic route was not practical for analog synthesis because of the harsh conditions and low yield on conversion of **88** to camptothecin. Furthermore, for drug discovery and development, racemic camptothecins are of limited use. Thus, a more practical 'second generation' asymmetric synthesis of camptothecin was developed.[55–57] The second generation synthesis featured: (1) using iodopyridone as a better substrate for the cascade radical annulation reaction, (2) construction of the E ring at early stage of synthesis and carrying it through the cascade radical annulation.

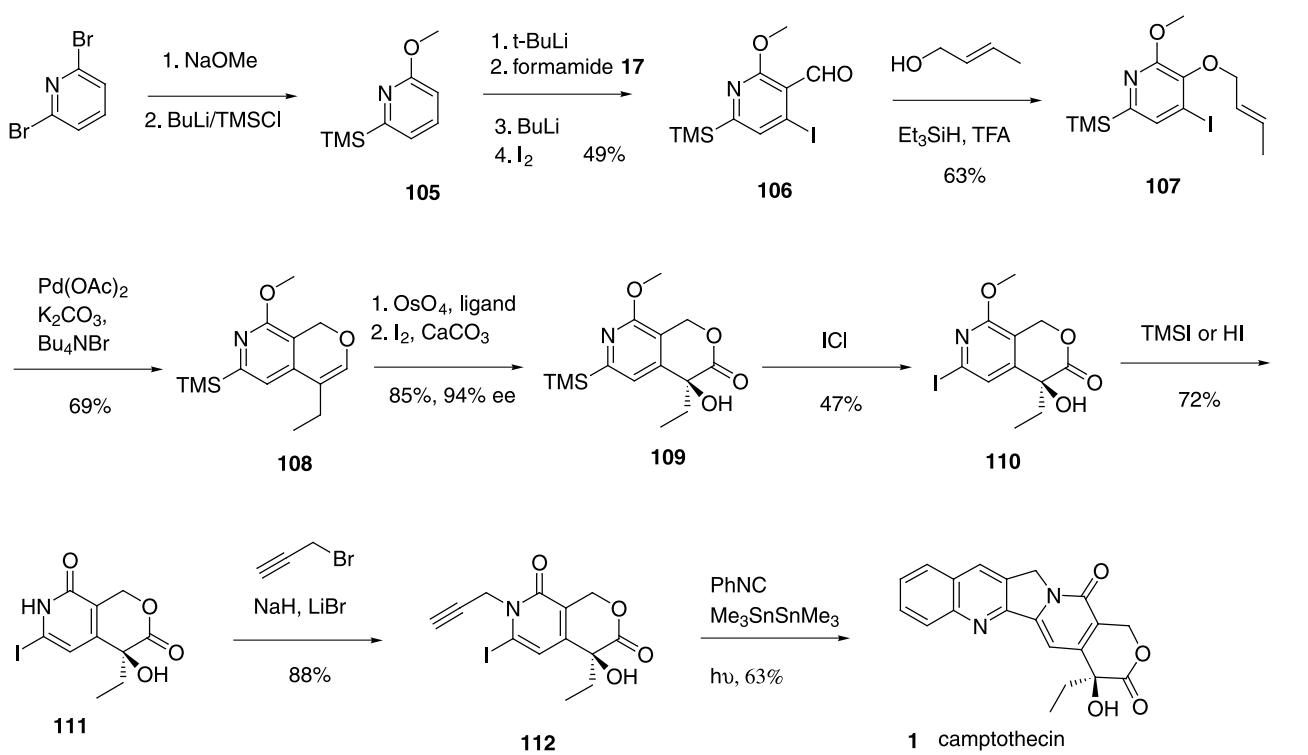
As shown in Scheme 20, Curran's synthesis and Glaxo Wellcome's synthesis shared the idea of construction of the α-hydroxy lactone E ring by an asymmetric dihydroxylation. To avoid carrying the iodide through multiple steps, a TMS group was used as its precursor. Treatment of



Scheme 19.

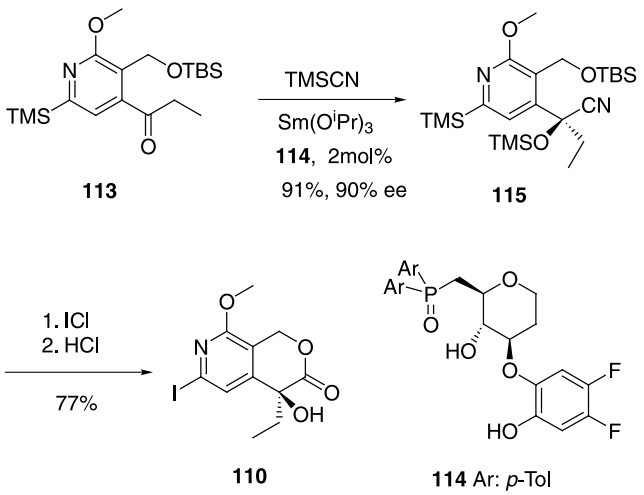
2,6-dibromopyridine with MeONa, BuLi/TMSCl yielded masked pyridine **105**. Following the procedure of Comins, **105** was sequentially treated with *t*-BuLi, formamide **17**, BuLi and I_2 to give pyridine **106** in 49% yield. Reductive etherification under Et_3SiH/TFA conditions yielded ether **107** which then underwent a Heck reaction to give a vinyl ether **108**. Conditions of Sharpless asymmetric dihydroxylation on vinyl ether **108** were then developed. In the presence of $(DHQD)_2PYR$ ligand, dihydroxylation of **108** gave a α-hydroxy lactol, which was then oxidized under $CaCO_3/I_2$ conditions to give lactone **109** in 85% yield and 94% ee. Treatment of lactone **109** with ICl gave a 1:1 mixture of iodopyridine **110** and unreacted **109**. The attempt to push iododesilylation to completion was not successful. Lactone **109** could be separated from product **110** and recycled. The methyl ether in lactone **110** was deprotected using TMSI generated in situ from TMSCl and NaI to give iodopyridone **111**. Subsequent propargylation and the radical annulation with phenyl isonitrile gave 20(*S*)-camptothecin in 63% yield.

As an alternative to the asymmetric dihydroxylation reaction, an efficient catalytic asymmetric cyanosilylation reaction was recently developed by Shibashaki, Curran and co-workers to prepare the key intermediate **111**.[58–60] Treatment of ketone **113** with TMSCN, 2 mol% $Sm(O^iPr)_3$ and Shibashaki's chiral ligand **114** yielded TMS protected cyanohydrin **115** in 91% yield and 90% ee. Iododesilylation



Scheme 20.

followed by an acid-catalyzed hydrolysis of the nitrile and spontaneous deprotection and lactonization gave lactone **110** in 77% yield. Subsequent demethylation and recystallization gave **111** with >99% ee (Scheme 21).



Scheme 21.

3.2. Synthesis of irinotecan and lurtotecan

Curran's asymmetric total synthesis of camptothecin demonstrated a highly divergent approach. Various substituents at 7-position of camptothecin can be introduced at the *N*-propargylation step. As shown in Figure 8, various substituents at positions 9–12 in A-ring can be introduced by using substituted phenyl isonitriles. The conditions for the final radical cyclization are very mild and can tolerate many functional groups. This approach allows access to many camptothecin analogs that are difficult or even impossible to prepare by other synthetic approaches, thus it is especially suitable for medicinal chemistry and SAR studies.

Regioselectivity as shown in Figure 8 is an interesting issue in this cascade radical annulation reaction. Reactions of 2-substituted phenyl isonitriles give 12-substituted camptothecins **119**, 4-substituted phenyl isonitriles give 10-substituted camptothecins **117**. 3-Substituted phenyl isonitriles usually give a mixture of 9 and 11-substituted camptothecins **116** and **118**. The formation of these two regioisomers is rationalized in Scheme 22. The 5-*exo* radical cyclization step gave two equilibrating conformers **121** and **122** of the resulting vinyl radical. Radical addition to phenyl ring of each conformer results in formation of **116** and **118**. The ratio between the two regioisomers depends on the substituents, but is usually close to 1:1. However, if both R and R^7 are large, the less sterically crowded **118** is sometimes favored.

Recently, Curran and Du disclosed that 2,6-disubstituted phenyl isonitriles could also participate in this cascade radical annulation and gave a mixture of **116** and **119**.[61] Interestingly, this reaction gave the sterically crowded product **106** as the major product and in most of the cases, the bulkier the substituents R^7 and R^9, the better the selectivity that favors **116**. A rationale for this counter-intuitive result is shown in Scheme 23. After formation of

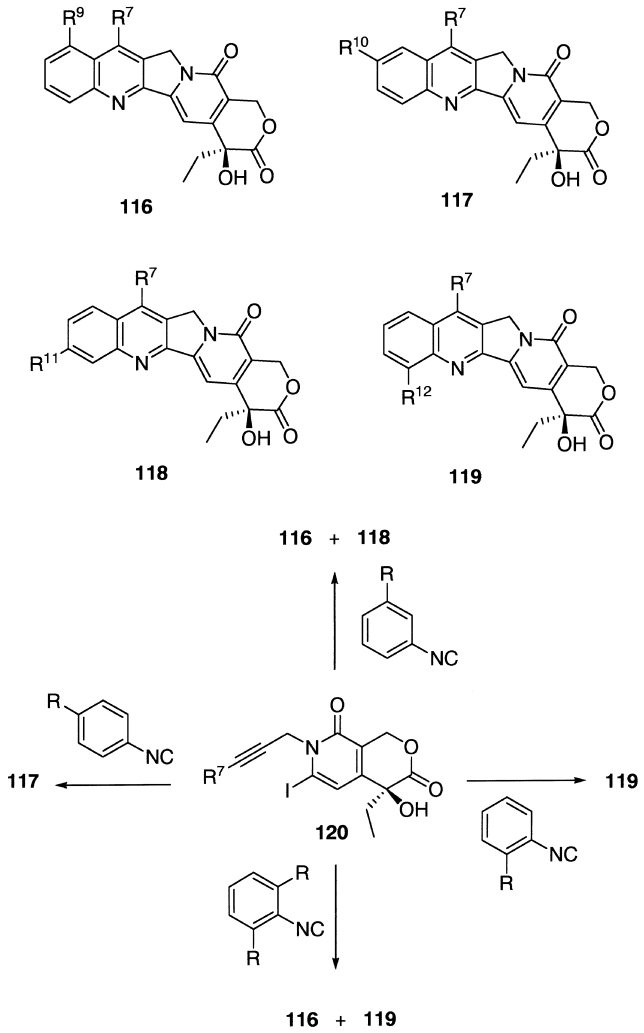
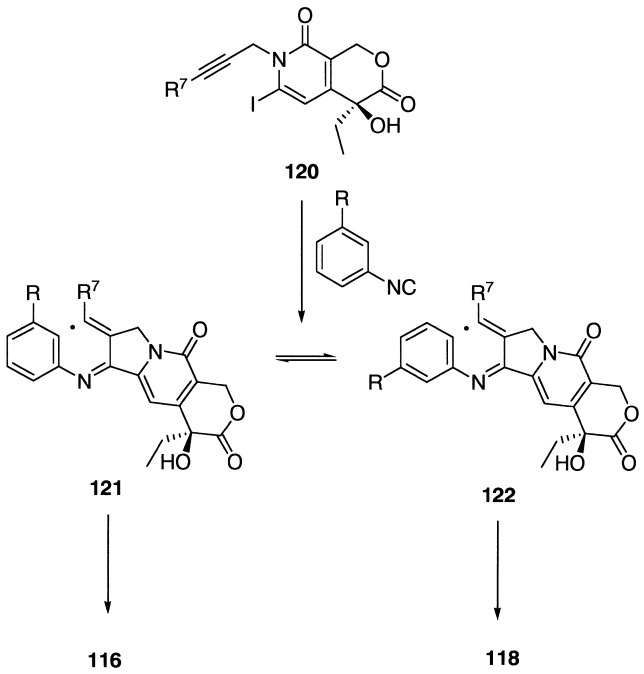
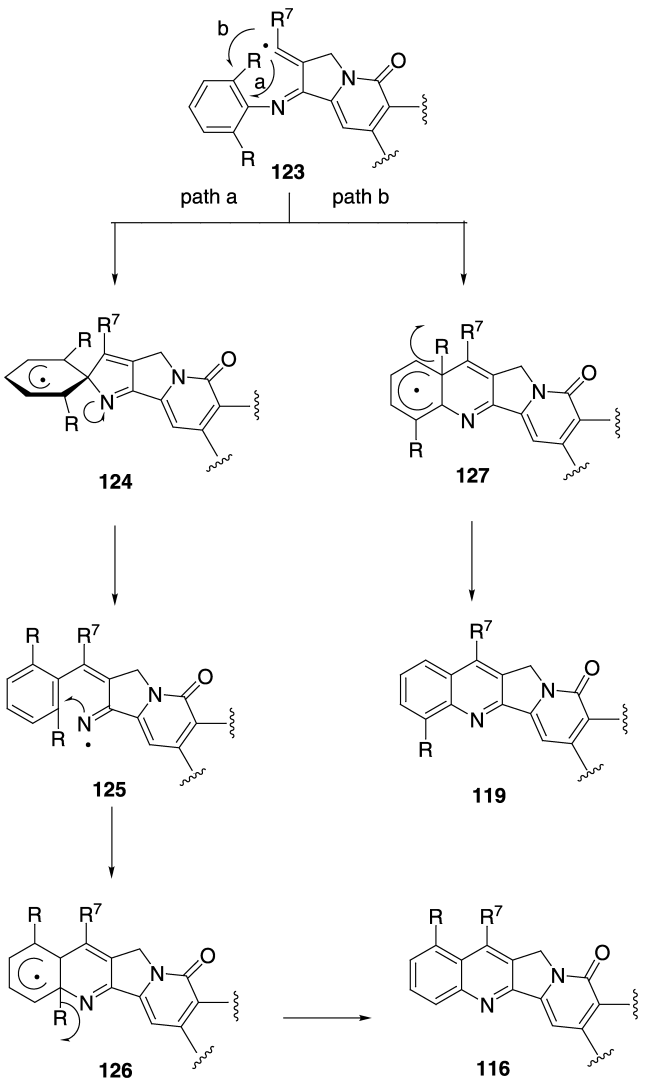


Figure 8. Regioselectivity in the 4+1 radical annulation reactions.



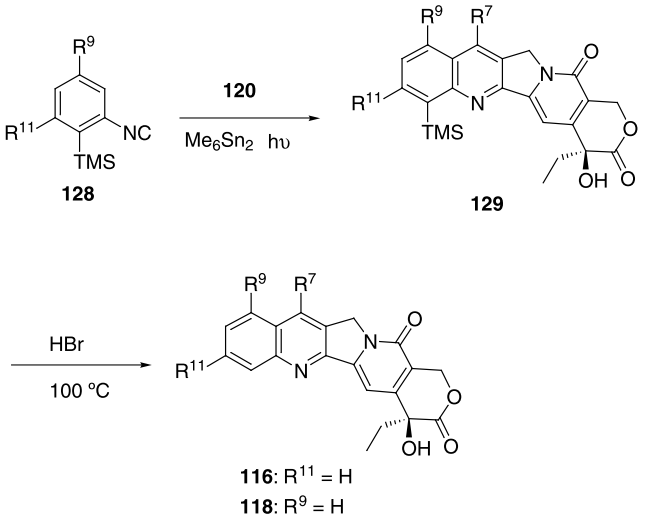
Scheme 22.



Scheme 23.

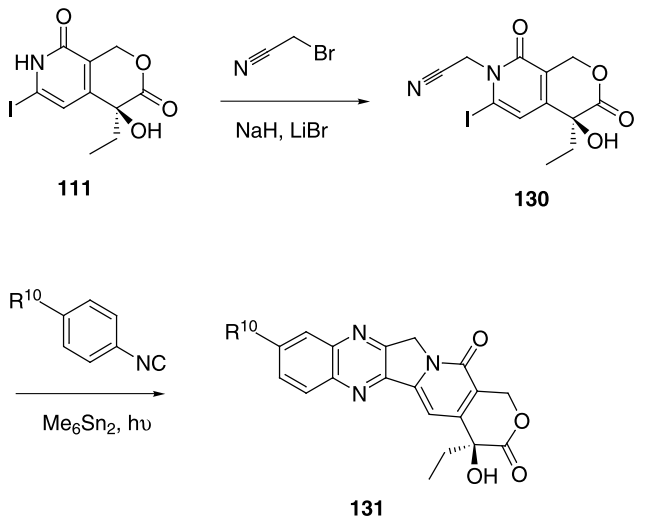
vinyl radical intermediate **123**, there are two pathways a and b for further radical addition. While pathway b is considered as the general pathway that accounts for the 'normal' cyclization product, pathway a was first proposed by Curran and Liu in 1991 as a minor reaction pathway that accounted for a quinoline side product.[60] Through pathway a, intermediate **123** undergoes a *ipso* (1,5) radical cyclization to give a spiro intermediate **124**, which then gives iminyl radical **125**. Subsequent *ortho* (1,6) cyclization gives intermediate **126**, which gives **116** after aromatization. In pathway b, *ortho* (1,6) cyclization followed by aromatization gives **119**. In these reactions, pathway a becomes the major pathway that allows less R–R^7 steric interaction by formation of a spiro intermediate **124**, which is less sterically crowded than **127**, although **124** leads to the more crowded final product **116**. This reaction was applied to regioselective synthesis of 7,9-disubstituted camptothecin analogs.

The formation of regioisomers in reactions using 3-substituted phenyl isonitrile promoted the Curran group to develop a regio-controlled synthesis of 9 and 11-monosubstituted camptothecins.[57] Their solution was to use a TMS group as a versatile blocking group. As shown in Scheme 24, reaction of silylphenyl isonitrile **128** with **120** gave camptothecin analogs **129**. Upon treatment with HBr at elevated temperature, the A-ring TMS group could be readily removed to yield a single product. Interestingly, silyl groups at the 7-position were not removed under these conditions. The price for improved regioselectivity is that extra steps are needed to prepare isonitrile **128**.



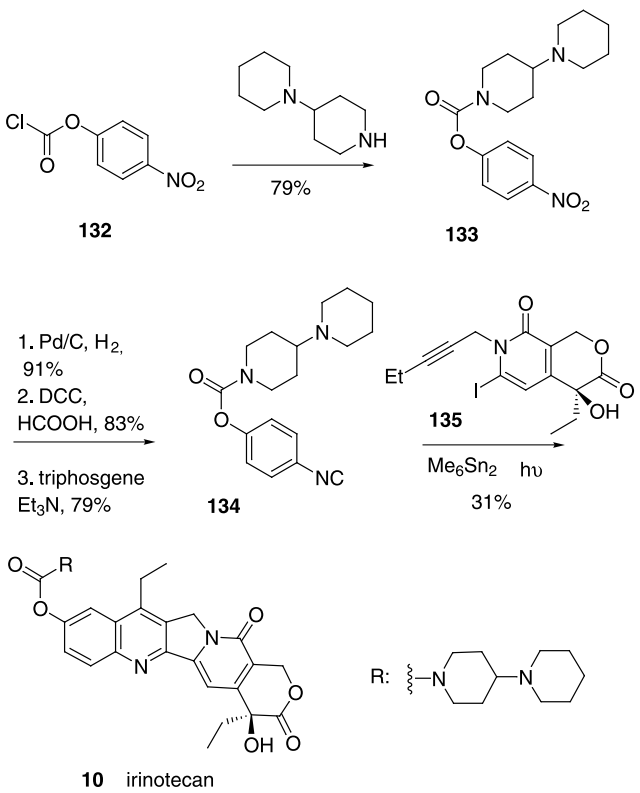
Scheme 24.

That a cyano group is susceptible to radical addition provides greater capability for this cascade radical cyclization approach to prepare camptothecin analogs. In the *N*-alkylation step, the propargyl bromide could be replaced with bromoacetonitrile to give iodopyridone **130**. Radical annulation using **130** and substituted phenyl isonitriles under the standard sunlamp irradiation conditions gave various 7-aza-camptothecins **131** (Scheme 25).



Scheme 25.

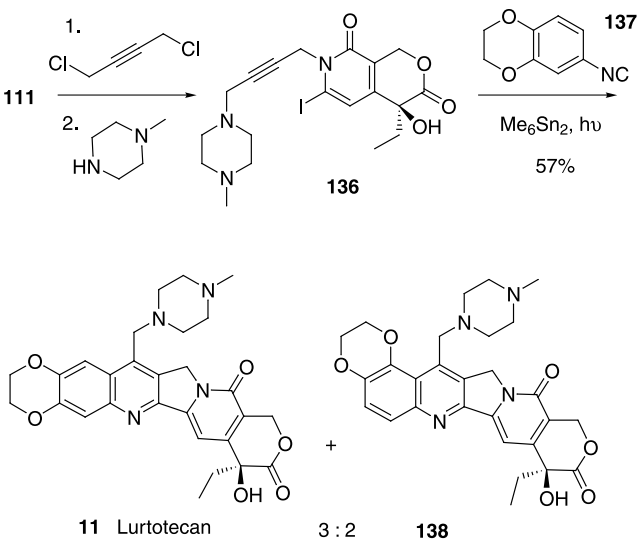
Applying the second generation asymmetric synthesis, the anticancer drug irinotecan and drug candidate lurtotecan were prepared.[55,57] The radical approach to irinotecan, as shown in Scheme 26, called for isonitrile **134** and iodopyridone **135**, which was easily prepared by alkylation of **111** with ethylpropargylbromide. Compound **132** was



Scheme 26.

converted to carbamate **133**, which was then reduced, formylated and dehydrated to give isonitrile **134**. The radical annulation of **134** and **135** under standard conditions yielded irinotecan **10** in 31% yield (Scheme 26). Irinotecan is a prodrug of its active metablite SN-38. While other syntheses of irinotecan used SN-38 as an intermediate, Curran's route avoided this highly toxic intermediate by direct formation of the prodrug.

The synthesis of lurtotecan is shown in Scheme 27.[55,57] Alkylation of **111** with 1,4-dichloro-2-butyne followed by treatment with *N*-methylpiperazine gave pyridone **136**. Radical annulation with isonitrile **137** gave a mixture of

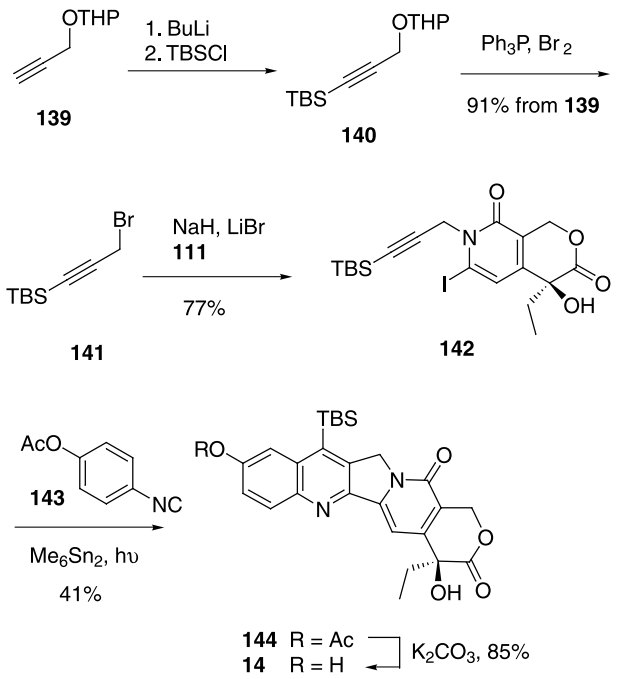


Scheme 27.

regioisomers **11** and **138** in a ratio of 3:2. The synthesis of these highly complex camptothecin analogs demonstrated the power of the cascade radical annulation strategy.

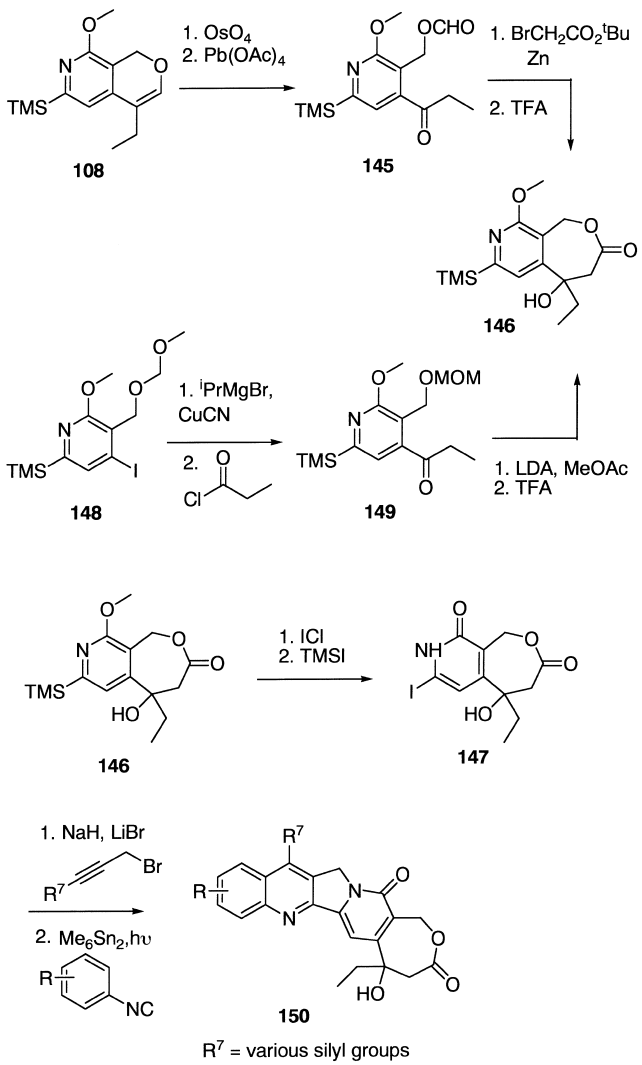
3.3. Synthesis of silatecan, homosilatecan and mappicine libraries

The powerful radical annulation approach is not limited to synthesis of known drugs and drug candidates. The highly divergent feature of this strategy makes it ideal for analogs synthesis and SAR studies. A collaborative drug discovery program based on the Curran group's second generation total synthesis resulted in the discovery of 7-silyl camptothecins (silatecans) as a new class of antitumor agent.[62] The synthesis of silatecans is straightforward. *N*-Propargylation of pyridone **111** with various silylpropargyl bromides followed by reaction of the resulting propargylated iodopyridones with substituted phenyl isonitriles under the standard radical cyclization conditions gave silatecans with substituents in A, B rings. For example, the synthesis of silatecan drug candidate DB-67 is shown in Scheme 29.[52,63] Treatment of THP protected propargyl alcohol **139** with BuLi followed by TBSCl gave **140**, which upon treatment with Ph_3P and bromine gave silylpropargyl bromide **141**. Alkylation of iodopyridone **111** with **141** gave iodopyridone **142**. Radical annulation of **142** with isonitrile **143** under the standard conditions yielded silatecan **144**. Drug candidate **14** (DB-67) was obtained in 85% yield by hydrolysis of **144** under K_2CO_3/MeOH conditions (Scheme 28).



Scheme 28.

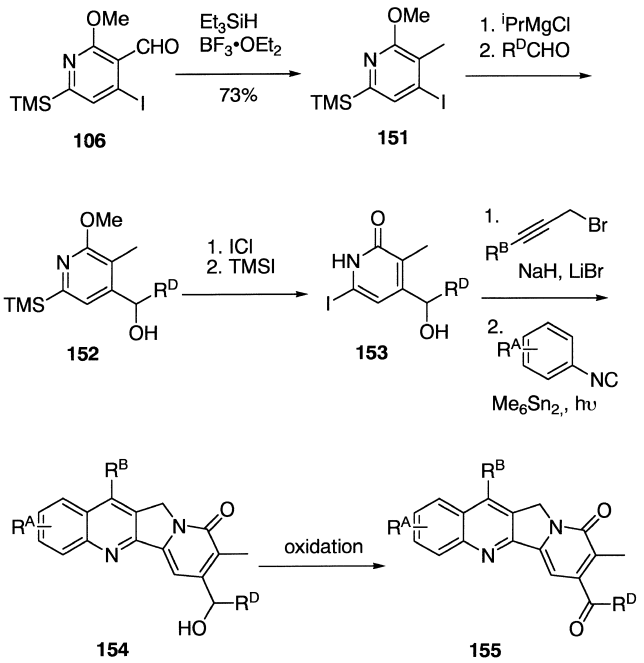
The discovery of homocamptothecin prompted Curran and co-workers to develop silatecans with homologated lactone E-ring, namely, homosilatecans.[64] The synthesis of homosilatecans called for the corresponding DE fragment with a homologated lactone. A racemic synthesis was first developed. As shown in Scheme 29, vinyl ether **108** was dihydroxylated by using OsO_4. The resulting diol was



Scheme 29.

treated with $Pb(OAc)_4$ to give ketone **145**. Reformatsky reaction on **145** resulted a β-hydroxy ester, which then lactonized upon treatment with TFA to give lactone **146**. Under previously developed conditions, the lactone **146** was converted to iodopyridone **147**. An alternative synthesis of **146** used pyridine **148**.[65] Sequential treatments of **148** with ^{i}PrMgBr/CuCN and proponyl chloride yielded ketone **149**, which underwent aldol reaction and lactonization to provide lactone **146**. With pyridone **147** in hand, combinatorial chemistry techniques were applied to generate homosilatecan libraries by reacting **147** with various silylpropargyl bromides and later, various phenyl isonitriles. Once again, the key radical annulation reaction demonstrated high compatibility and reliability. Libraries with over one hundred homosilatecan analogs **150** were readily synthesized by using parallel synthesis and automated purification.[65] These analogs are being screened for human blood stability, cytotoxicity and Topo I inhibition activity.

The development of new leads for antiviral drugs from mappicine analogs also took the advantage of the combinatorial features of Curran's cascade radical annulation reaction. A modified reaction sequence and conditions were used to prepared mappicine and mappicine ketone libraries.[66] As shown in Scheme 30, reduction of aldehyde **106** with Et_3SiH and $BF_3{\cdot}OEt_2$ yielded pyridine **151**. Treatment of **151** with ^{i}PrMgCl followed by various aldehydes gave alcohols **152**. Then the TMS group was replaced with iodine and the methyl ether was cleaved to give iodopyridones **153**. Subsequent propargylation with various propargyl bromides and cascade radical annulation with various phenyl isonitriles gave mappicine analogs **154** with different substituents R^A, R^B and R^D. Some of the mappicine analogs were oxidized to give a library of mappicine ketones **155**. Using the modified procedures, the natural product mappicine was also prepared in >95% ee, and the final radical annulation using *N*-propargylated iodopyridone occurred in 64% yield. The synthetic route is general and flexible, and it also demonstrates the advantage of strategically employing a cascade reaction at late stage of a synthesis.



Scheme 30.

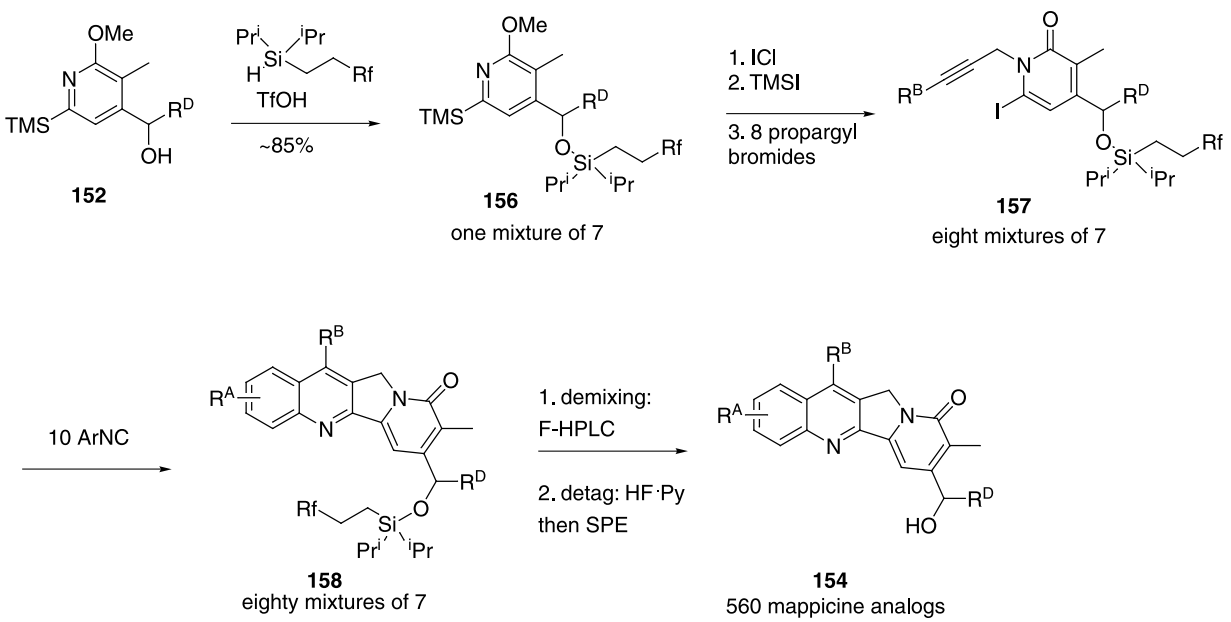
Recently, Curran and co-workers introduced the pioneering concept of fluorous mixture synthesis.[67] This was demonstrated by simultaneous synthesis of the both enantiomers of mappicine[68] and later, the synthesis of mappicine libraries.[69] The fundamental concept is that a collection of substrates can be tagged with fluorous chains with different lengths. This collection of substrates is then mixed together and taken through a multiple-step reaction sequence. After each reaction, the products are easily isolated by solid-phase extraction on fluorous silica gel.[70] At the end of the reaction sequence, the product mixture, still with their fluorous tags, can be purified and separated by HPLC on fluorous column. The retention time of each product in fluorous HPLC is mainly determined by the fluorine content in its fluorous tag. Thus, the mixture of products can be separated according to their fluorous tag. Finally, pure product is generated after detagging. This technique allows simultaneous synthesis of several compounds in one pot and gives each product in pure form. The advantages of this technique, such as high

efficiency, ease of intermediate characterization, and ease of transfer of conditions from traditional reactions, are demonstrated in synthesis of mappicines.

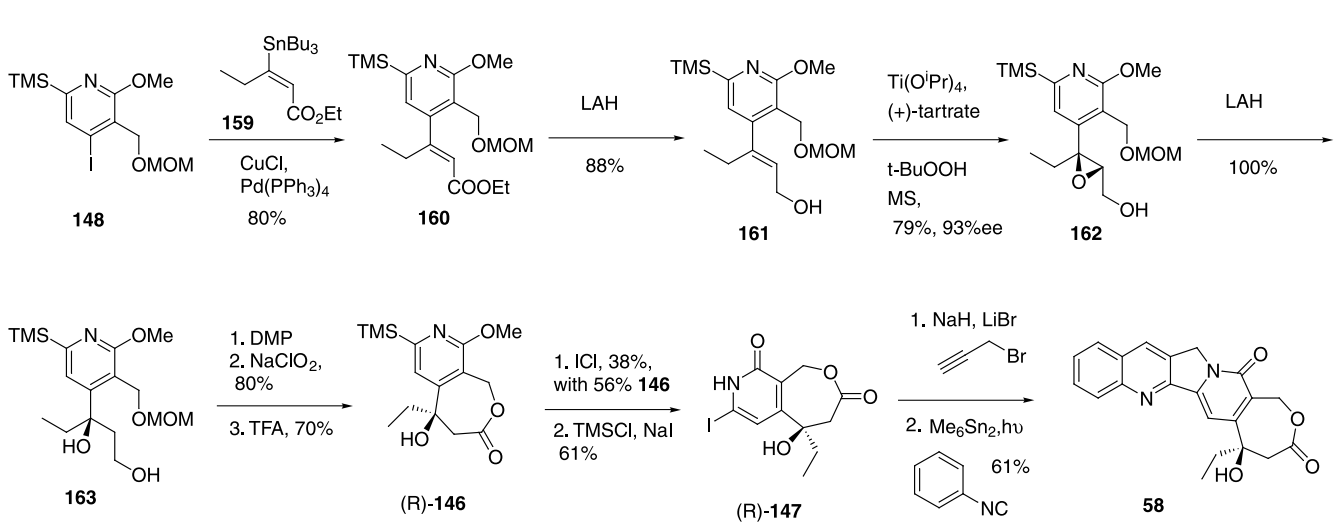
This concept was applied to simultaneous synthesis of both enantiomers of mappicine. Both enantiomers of **152** (R^D=Et) were tagged with different fluorous silyl group respectively, and then mixed together. After the reaction sequences, HPLC separation and detagging gave the two enantiomers of **6**.[68] A similar strategy was applied to synthesis of mappicine libraries with different substituents R^A, R^B and R^D. An efficient synthesis of a 560-member mappicine library was recently reported by chemists in Fluorous Technologies Inc.,[71] a company founded to commercialize various fluorous technologies. As shown in Scheme 31, **156** as a mixture of seven tagged pyridines was converted to a mixture of seven corresponding iodopyridones, which was then split and reacted with eight propargyl bromides to give eight mixtures of seven propargylated iodopyridones. The eight mixtures were split again and reacted with 10 aryl isonitriles to give eighty mixtures of seven tagged mappicines. Each mixture of seven compounds was demixed and detagged to give seven mappicines. Thus the synthesis of this 560-membered library used total 90 reactions, compared to 630 reactions needed by parallel synthesis. This combination of cascade radical reaction with fluorous mixture synthesis was discussed in Zhang's recent review on fluorous technologies.[72]

3.4. Asymmetric synthesis of (+)-homocamptothecins and synthesis of E ring analogs

The further development of homosilatecan drug candidates required preparation of homosilatecans in enantiomerically pure form, which called for enantiomerically pure (*R*)-**147**. The resolution approach shown in Scheme 12 is less attractive since it wastes half of the material. An asymmetric synthesis of (*R*)-**147** was developed using a modified Stille reaction and a Sharpless asymmetric epoxidation as the key reactions (Scheme 32).[73]



Scheme 31.



Scheme 32.

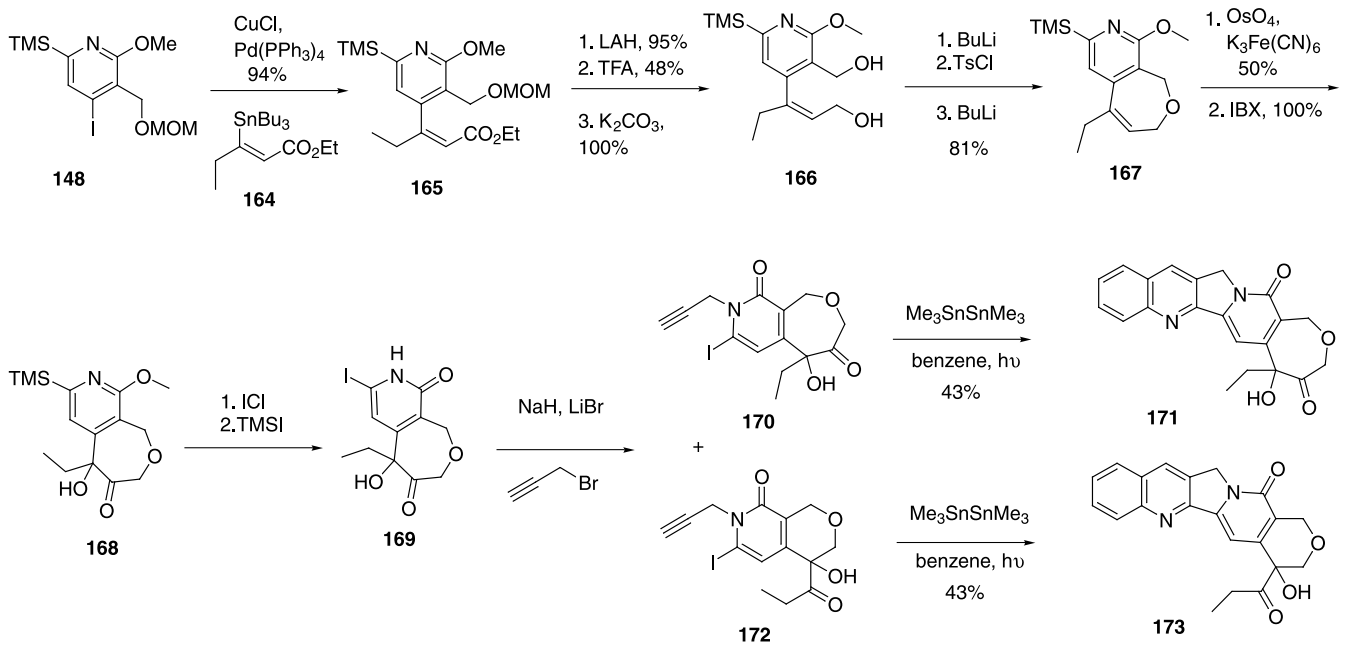
Under Corey's modified conditions for Stille reaction,[74] iodopyridine **148** reacted with known *trans*-vinyl stannyl compound **159** to give an ester **160**. The α,β-unsaturated ester was then reduced with LAH to give an allylic alcohol **161** for asymmetric epoxidation. The protocol of a Sharpless asymmetric epoxidation using stoichiometric titanium reagent and molecular sieves yielded epoxide **162** in 79% yield and 93% ee. The epoxide was then reduced with LAH to give a 1,3-diol **163**. The primary alcohol was then oxidized to a carboxylic acid. Treatment with TFA cleaved the MOM protective group and effected simultaneous lactonization to give (*R*)-**146**. Using conditions established before, (*R*)-**146** was converted to (*R*)-**147**. After subsequent propargylation with propargyl bromide and radical annulation with phenyl isonitriles, (+)-homocamptothecin **58** was obtained in 61% yield. Under similar conditions, (*R*)-**147** led to a number of enantiomerically enriched homocamptothecins and homosilatecans.

The success of homocamptothecin prompted Curran and co-workers to reconsider the potential of E-ring modification. Recently Curran, Burke, and co-workers reported the synthesis and evaluation of a novel α-hydroxy ketoether analog **171**, which has a seven-membered cyclic α-hydroxy ketoether E ring.[75] The synthesis was based on the radical annulation reaction and is shown in Scheme 33.

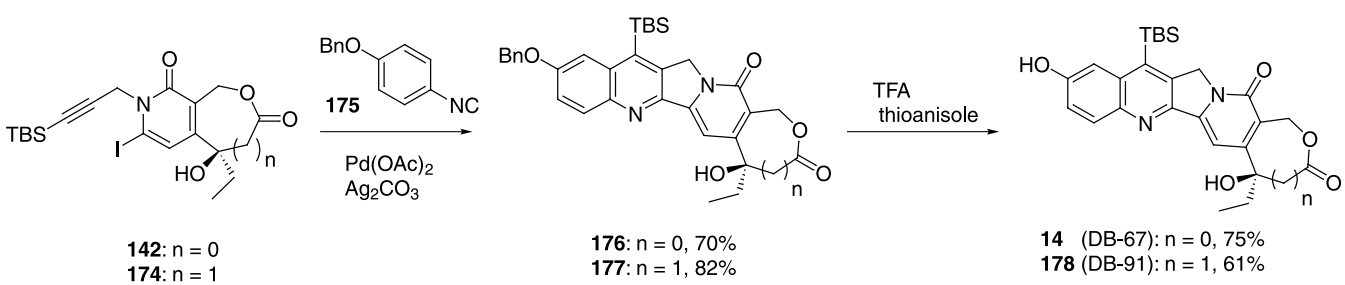
Iodopyridine **148** reacted with *cis*-stannyl compound **164** under Corey's Stille reaction conditions to give a *cis*-ester **165**. It was then reduced with LAH to give a *cis*-allylic alcohol, which then yielded diol **166**. Under BuLi/TsCl conditions, diol **166** cyclized to give an ether **167** in 81% yield. Allylic ether **167** was dihydroxylated to give a 1,2-diol, which was then oxidized under mild conditions to give a ketoether **168**. Subsequent iododesilylation and deprotection of the methyl ether yielded iodolactone **169**. Interestingly, the propargylation of **169** under NaH, LiBr conditions yielded two isomeric products, the desired **170** and a rearranged product **172**. Both iodopyridones were subjected to the radical annulation conditions to give respectively the expected ketoether analog **171** and a rearranged analog **173**. Both analogs were tested for cytotoxicity and Topo I inhibition activity. Unfortunately, although the keto ether analogs are highly stable in human blood, they showed little or no cytotoxicity.

3.5. Pd Promoted cascade reaction of aryl isonitriles

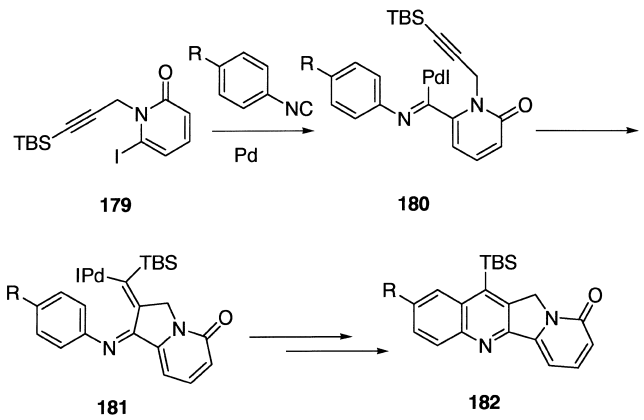
In searching for an alternative method to construct the B, C rings of camptothecin, Curran and Du discovered that a cascade reaction between an electron-rich aryl isonitrile and a propargylated iodopyridone could be promoted by a Pd catalyst to give the desired polycyclic quinoline product.[76] This reaction was applied to synthesis of silatecan and



Scheme 33.



Scheme 34.



Scheme 35.

homosilatecan drug candidates. As shown in Scheme 34, stirring isonitrile **175** with iodopyridone **142** or **174** in the presence of 20–30% $Pd(OAc)_2$ and 1–1.5 equiv. of Ag_2CO_3 gave **176** and **177** in 70–80% yield. Subsequent deprotection of the benzyl ether in TFA and thioanisole gave drug candidates **14** (DB-67) and **178** (DB-91).

The detailed mechanism of this process is not clear, but we speculate that palladium species are involved as intermediates. Although the same products could be obtained through a Pd initiated radical mechanism, the radical mechanism was excluded by a competition experiment using 2,6-disubstituted phenyl isonitrile. The proposed mechanism is shown in Scheme 35. Oxidative addition of a Pd catalyst to iodopyridone **179** followed by isonitrile insertion gives imidoyl palladium species **180**. Subsequent addition to triple bond gives vinyl palladium species **181**, which upon oxidative addition to aromatic C–H bond or addition to the aromatic ring, and followed by reductive elimination of palladium hydride gives product **182**.

3.6. Bowman's nitrile radical cyclization

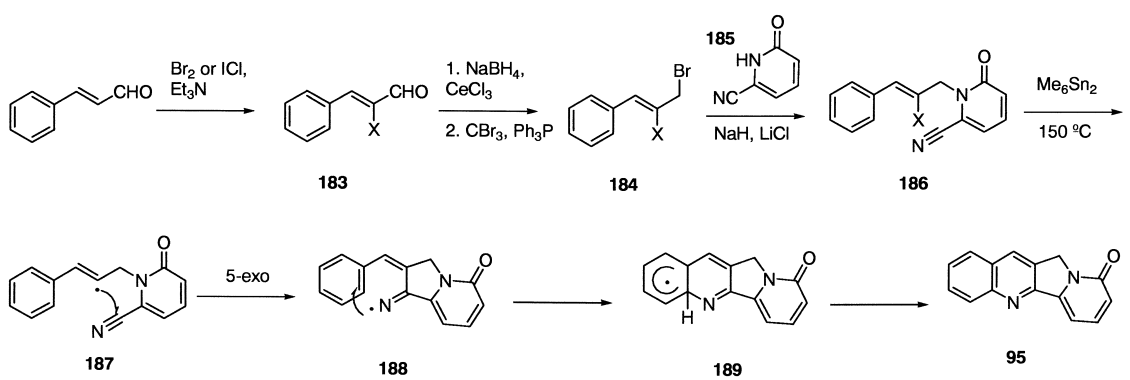
In their 1991 paper reporting the 4+1 radical annulation reaction, Curran and Liu observed a minor radical pathway, which involved formation of an iminyl radical and subsequent addition to the phenyl ring to give a cyclopenta-fused quinoline structure.[50] Recently, the Bowman group reported a synthesis of camptothecin model by a related cascade radical cyclization in which the iminyl radical was generated by radical addition to a cyanide group.[77] As shown in Scheme 36, treatment of cinnamaldehyde with Br_2 or ICl and triethyl amine produced **183** in which X can be either Br or I. The aldehyde was then reduced and the resulting allylic alcohol was converted to an allylic bromide **184**. Under NaH, LiCl conditions, cyanopyridone **185** was alkylated with allylic bromide **184** to give **186** as the precursor for radical cyclization. Heating **186** with hexamethylditin generated vinyl radical intermediate **187**, which then underwent 5-*exo* radical cylization to the cyano group to give an iminyl radical **188**. Intramolecular radical addition of **188** produced the delocalized radical **189**, which was then oxidized to give the highly conjugated quinoline **95**. In addition to the model compound of camptothecin, a number of polycyclic quinolines were prepared by this method.[78] If successfully applied to the synthesis of camptothecin, Bowman's cascade radical cyclization may provide a unique approach to 9-substituted camptothecin analogs.

4. The Friedlander condensation approach (B-ring construction)

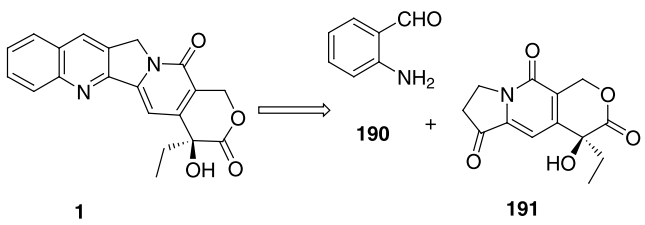
Friedlander condensation is a well-established reaction used to construct quinolines. This reaction has been used in total synthesis of camptothecin during the 1960s and 1970s by Stork, Danishefsky, Rapoport and Chinese chemists as summarized in Hutchinson's 1981 review.[4] In the early 1990s, excited by the new discovery on camptothecin's mechanism of action, medicinal chemists were in a hurry to access various camptothecin analogs while new syntheses of camptothecins were under development. The Friedlander condensation became a popular approach for analog synthesis because of its reliability. Recent developments on Friedlander condensation based approaches focused on asymmetric synthesis of camptothecin and application in synthesis of camptothecin analogs.

4.1. Synthesis of (+)-camptothecin and modified synthesis of (±)-camptothecin

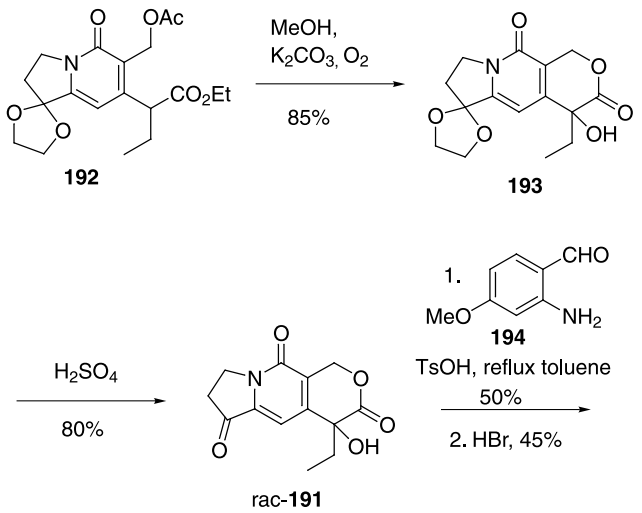
The most efficient application of the Friedlander condensation is reaction of amino aldehyde **190** or its imine equivalent with the tricyclic ketone **191** (Scheme 37). Wani, Wall and their co-workers first reported synthesis of racemic camptothecins using racemic **191** in 1986.[79] In following syntheses, much effort was spent on preparation of enantiomericly pure **191**.



Scheme 36.



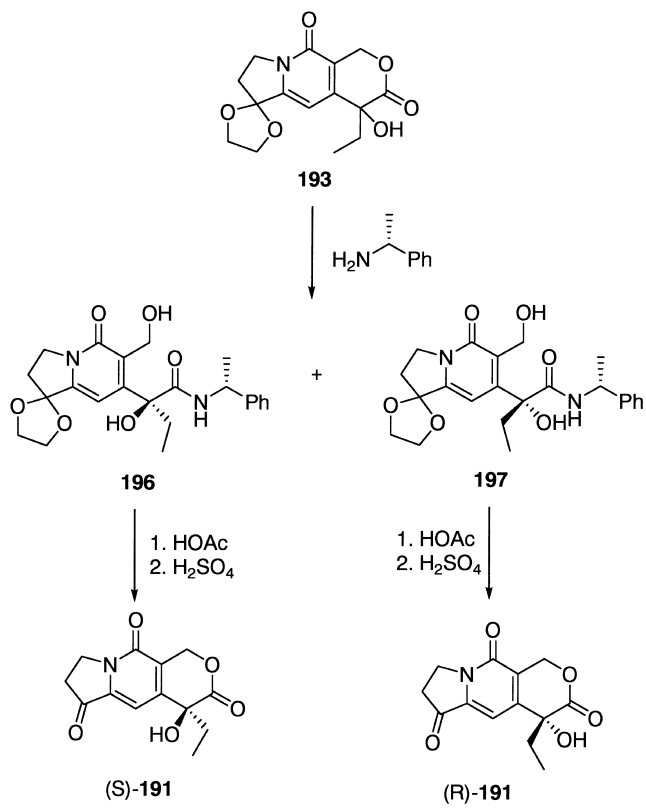
Scheme 37.



Scheme 38.

Wani and Wall's synthesis of **191** is shown in Scheme 38. Oxygenation of **192**, a known intermediate from Wani and Wall's previous synthesis, and one-pot removal of acetate and lactonization gave lactone **193**, which upon treatment with aqueous H_2SO_4 gave racemic **191** in 80% yield.[79] Under Frieldlander condensation conditions (catalytic amount of TsOH, reflux in toluene), **191** reacted with aldehyde **194** to give 11-methoxycamptothecin, which upon treatment of 48% HBr gave natural product 11-hydroxy-camptothecin **195**. After being applied to analog synthesis,[79–82] a resolution procedure was developed by the same group to obtain (*S*)-**191**, which subsequently yielded 20(*S*)-camptothecins.[82] As shown in Scheme 39, reaction of racemic **193** with (*R*)-(+)-α-methylbenzylamine yielded two diasteromers **196** and **197**, which were readily separated. Treatment of **196** and **197** with hot acetic acid gave (*S*)-**191** and (*R*)-**191**, respectively. Their configurations were confirmed by converting them to 20(*S*)- and 20(*R*)-camptothcins.

The Tagawa group reported an asymmetric synthesis of **191** using an ethylation reaction in the presence of an ester chiral auxiliary.[83,84] Pyridone **198** was brominated to give

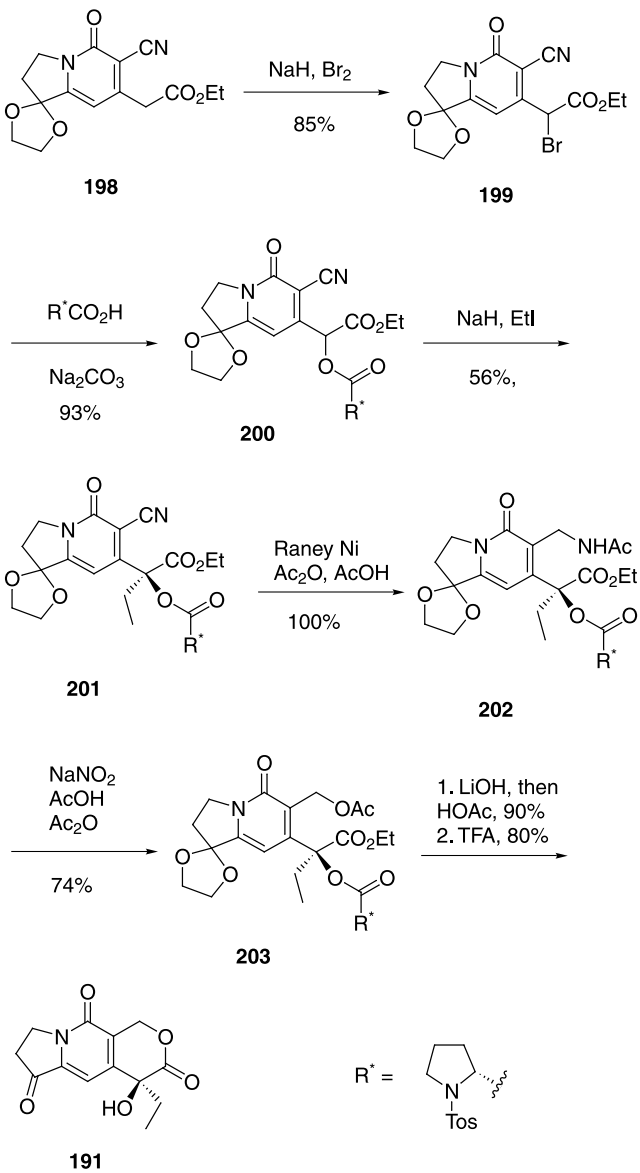


Scheme 39.

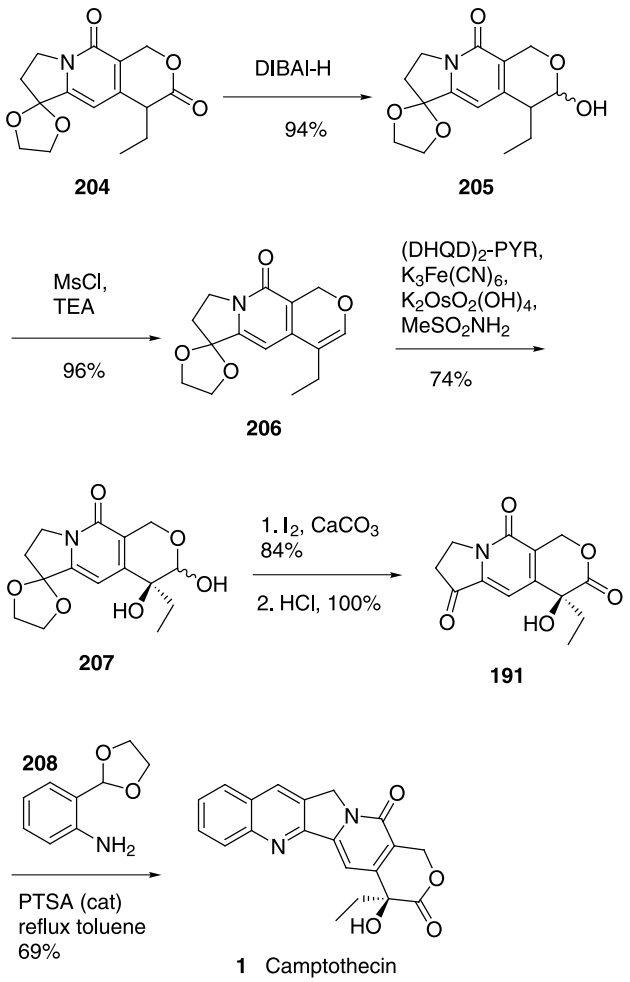
bromide **199**. Treatment of **199** with *N*-tosyl-(*R*)-proline and base gave ester **200**. The proline ester functioned as a chiral auxiliary and a masked hydroxy group. Asymmetric ethylation of **200** by treatment with NaH and EtI gave **201** and its diastereomer with a de of 64%. The diastereomer was easily separated from **201**. The cyano group was then reduced by Raney Ni and was acetylated in one-pot. The acetamide **202** was converted to acetate **203** under $NaNO_2$, HOAc, Ac_2O conditions. Subsequent hydrolysis and acid treatment gave (*S*)-**191** (Scheme 40).

Sharpless asymmetric dihydroxylation was also applied to synthesis of **191**. The Jew group reported an enantioselective synthesis of camptothtecin using this approach.[85] As shown in Scheme 41, DIBAL-H reduction of latone **204** followed by mesylation and elimination gave vinyl ether **206** for dihydroxylation. A number of ligands were tested. The best results were obtained using $(DHQD)_2$–PHAL and $(DHQD)_2$–PYR, which gave lactol **207** in 84% ee and 60–80% yield. Subsequent oxidation and removal of the acetal protective group gave the desired lactone **191**. Frieldlander condensation of **191** with an acetal protected amino aldehyde gave camptothecin in 69% yield.

An asymmetric hydroxylation reaction was also applied to install the 20-(*S*)-hydroxy group of camptothecin.[86] Friedlander condensation between **204** and 2-formyl aniline gave 20-deoxycamptothecin **2**. This compound was enolized by treatment with $LiN(TMS)_2$. Subsequent treatment with Davis's chiral oxaziridine **102** gave enantiomerically enriched **1**. The ee of this reaction was not reported. It can be roughly estimated based on reported optical rotations to be around 40–50% (Scheme 42).



Scheme 40.

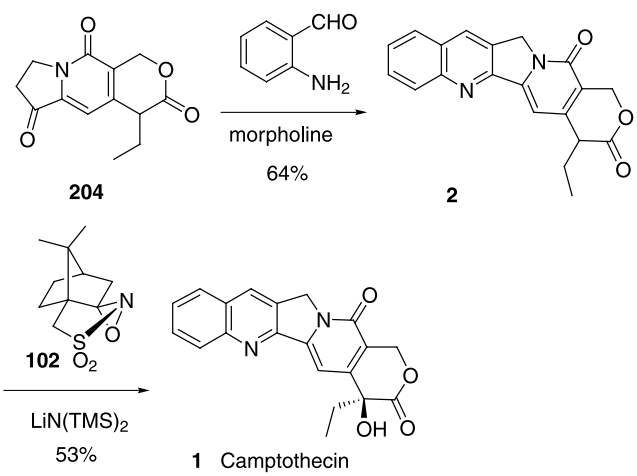


Scheme 41.

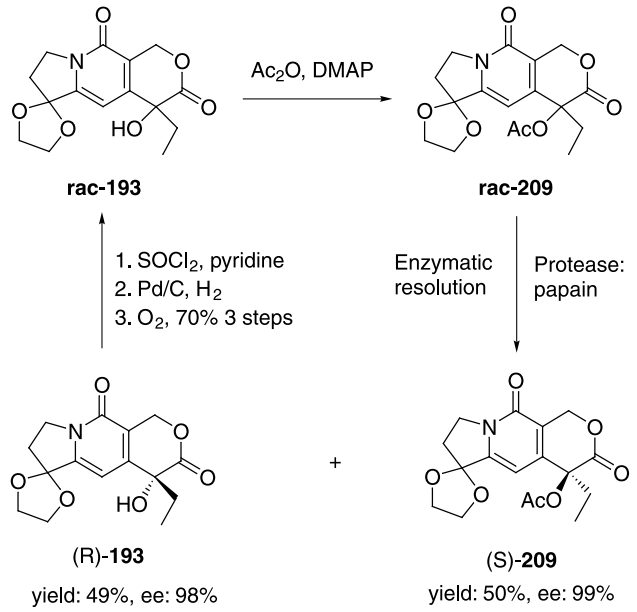
Enzymatic resolution was also used by the Imura group to obtain enantiomericly pure material.[87,88] Over a hundred of commercially available enzymes, including lipases, esterases and proteases, were screened for enantiomeric hydrolysis of acetate **209**. A commercially available protease, papain from papaya, was found to be the right enzyme for **209**. Under the optimum conditions: **209** and papain in pH 6.5 phosphate buffer with EtOAc as co-solvent at 40°C, (*R*)-**193** was obtained in 49% yield and 98% ee while (*S*)-**209** was obtained in 50% yield and 99% ee. Changing acetate to other esters resulted in lower conversion and lower ee for (*S*)-**209**. (*R*)-**193** was recycled through a three-step sequence to give racemic **193**. Hydrolysis of (*S*)-**209** followed by deprotection of the acetal gave (*S*)-**191** for Friedlander condensation (Scheme 43).

The Tagawa group reported another procedure to recycle the seemingly wasted (*R*)-**193** by inverting the *R* configuration to *S* configuration (Scheme 44).[89] (*R*)-**193** was treated with MsCl to give a methanesulfonate **210**. Subsequent treatment with CsOAc inverted the tertiary chiral center to give (*S*)-**209** in 33% yield. Interestingly, when NaOAc or KOAc was used, the reaction did not proceed. Although low yielding, this provides a rare example of inverting the configuration of a tertiary alcohol.

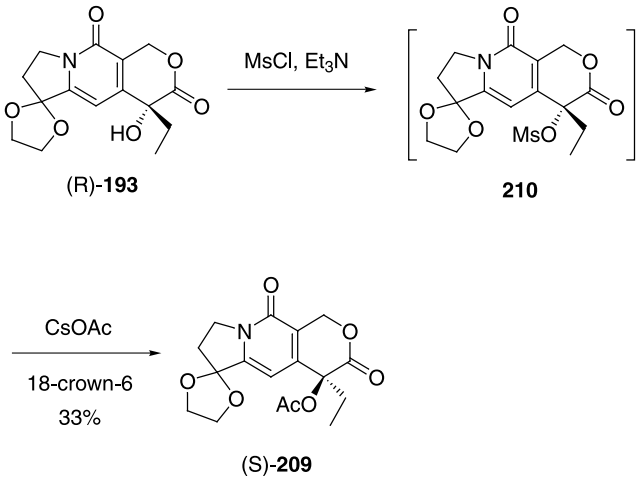
The total synthesis of racemic camptothecin reported by Shen, Danishefsky and co-workers focused on



Scheme 42.



Scheme 43.

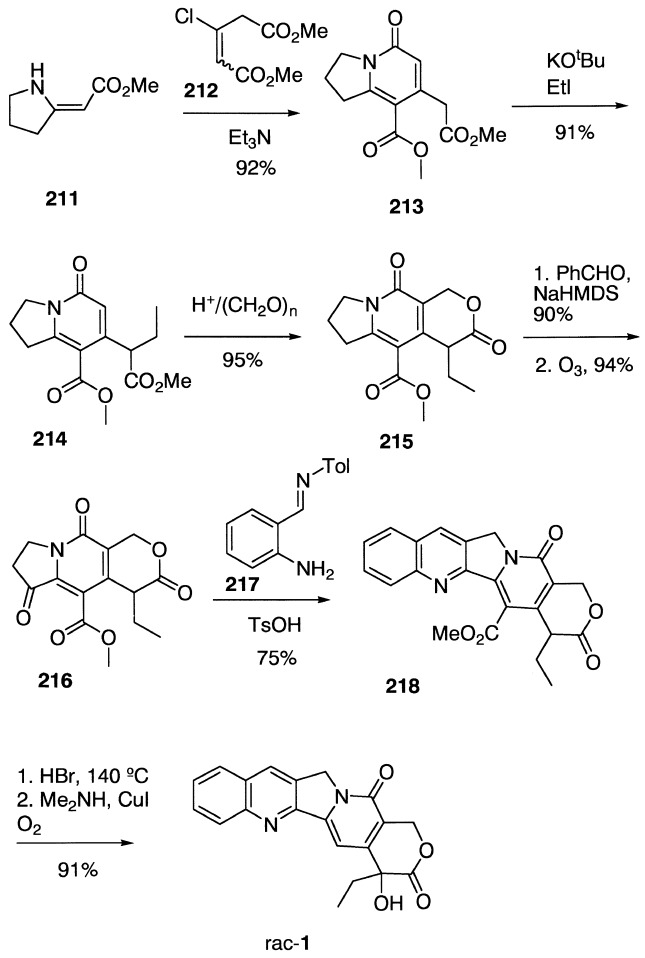


Scheme 44.

modifications to improve the overall yield of Daneshefsky's original synthesis.[90] Annulation of vinylogous urethane **211** with an allene generated in situ from **212** gave pyridone **213**. Ethylation followed by a hydroxymethylation and lactonization gave lactone **215**. Then several routes were studied to convert **215** to camptothecin. The most high-yielding one is shown in Scheme 45. Treatment of **215** with NaHMDS and benzaldehyde gave an olefin product, which upon ozonolysis yielded ketone **216** in high yield. Friedlander condensation of **216** and Shiff base **217** gave quinoline **218** in 75% yield. Decarboxylation was achieved by heating **218** with HBr at 140°C to give 20-deoxycamptothecin **2**, which was converted to racemic camptothecin in 91% yield by hydroxylation.

4.2. Pharmacia & Upjohn's total synthesis of irinotecan

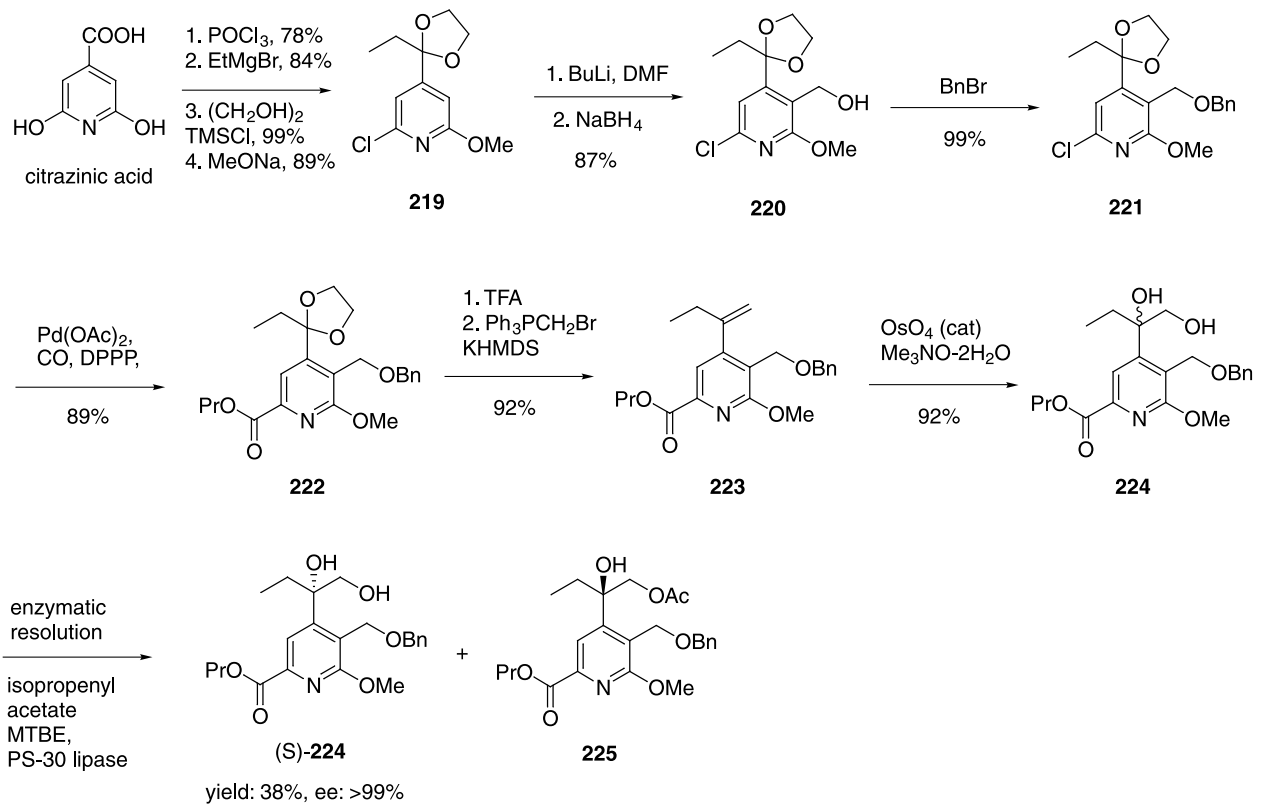
Irinotecan was licensed for sale in the US by Pharmacia & Upjohn from Yakult Honsha. In addition to a five-step semi-synthesis developed by Sawada (20% overall yield),



Scheme 45.

Henegar and co-workers in Pharmacia & Upjohn developed a scaleable total synthesis of irinotecan with 18 steps and 6% overall yield.[91] Their synthesis used an enzymatic resolution method to obtain the tertiary alcohol with high ee, and a Friedlander condensation to build the quinoline ring.

Pharmacia & Upjohn's route started from citrazinic acid. Chlorination followed by an EtMgBr addition provided an ethyl aryl ketone. Protection of the ketone as a ketal followed by replacing a chloride with methoxy group gave methyl ether **219**. Regio-selective deprotonation of **219** with BuLi in nonpolar solvent followed by reaction with DMF yielded an aldehyde, which was then reduced with $NaBH_4$ to give alcohol **220** in 87% yield. The alcohol was protected to give benzyl ether **221**. Palladium-catalyzed carbonylation provided **222** in 89% yield. Then the ketal was deprotected and the resulting ketone underwent a Wittig reaction to give olefin **223**. Asymmetric dihydroxylation was first attempted on this compound; however, the observed 68% ee was deemed too low. Therefore, an enzymatic resolution was used instead. Catalytic dihydroxylation of **223** gave a racemic diol **224** in 92% yield. The resolution was achieved by an acetylation of the racemic diol with isopropenyl acetate and using Amano PS-30 lipase as a catalyst. The reaction yielded (*S*)-**224** in 38% yield and >99% ee. Acetate **225** could be converted back to **223** though a three-step, one-pot process (Scheme 46).



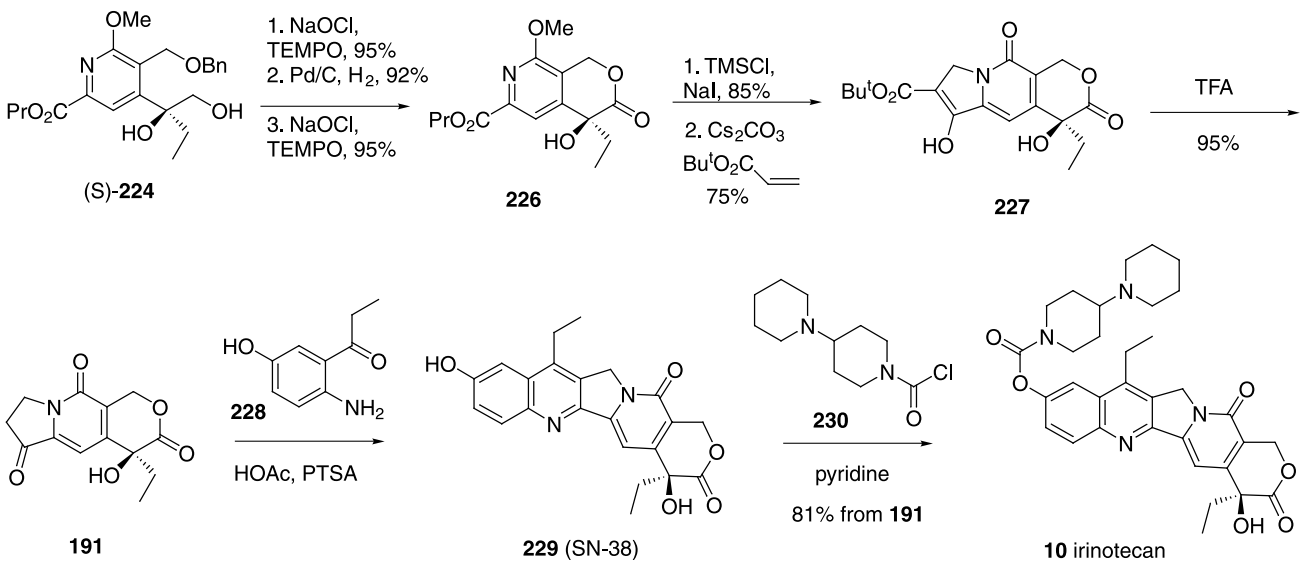
Scheme 46.

Alcohol (*S*)-**224** was then oxidized and deprotected to give a lactol, which was oxidized again to give lactone **226**. Deprotection of the methyl ether followed by a Michael addition and Dieckmann condensation reaction provided ester **227** in 75% yield. Deprotection of the *t*-butyl ester with TFA and decarboxylation of the resulting carboxylic acid gave ketone **191**. Subsequent Friedlander condensation with aniline **228** gave **229**, which is the actual drug formed in vivo from the prodrug irinotecan. Compound **229** is also known as SN-38. Acylation of **229** with **230** provided irinotecan with >99.8% ee and 81% yield from **191** (Scheme 47).

The Pharmacia & Upjohn's route was performed on a laboratory scale to give irinotecan with >99.5% ee and 6.4% overall yield in 18 chemical steps without counting the recycle of **225**. The synthesis uses cheap and easily available starting materials and the operation is easy to perform. This route was scaled up and the initial piloting provided >35 kg of intermediate **227**.

4.3. Application in synthesis of analogs, drug candidates and camptothecinoids

The Friedlander condensation approach is general and



Scheme 47.

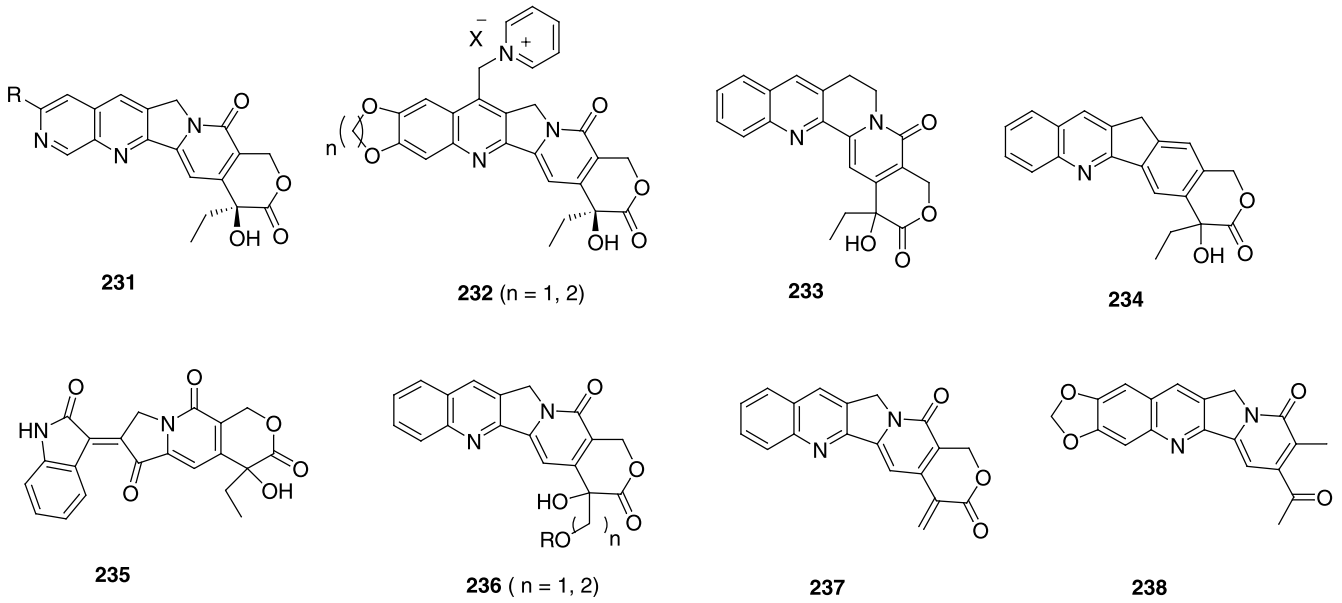


Figure 9.

provides access to many camptothecin analogs. A, B ring analogs can be prepared by condensation of **191** with various substituted amino ketones or aldehydes. E-ring analogs can be prepared by condensation of an amino ketone or amino aldehyde with modified versions of ketone **191**. While these analog syntheses will not be discussed here in detail, some examples of A, B, C, D and E rings modified analogs prepared by this approach are shown in Figure 9 to demonstrate the broad scope of application of this synthetic approach. They include A-ring analog 11-azacamptothecin **231**,[92] AB rings modified analogs **232**,[93] C ring expanded analog **233**,[94] D ring analog **234**,[95] rigid analog **235**,[96] E ring analogs **236**,[97] **237**[98] and mappicine analog **238**.[27] These analog syntheses largely accelerated lead discovery and anticancer drug development of camptothecin family.

A number of drug candidates were first identified among analogs prepared by this approach. As shown in Figure 10, Friedlander condensation of **191** with corresponding amino ketones or aldehyde led to drug candidates lurtotecan **11**,[99] exatecan **12**,[100,101] **239** (CKD-602),[102,103] natural products 9-β-D-glucosyloxy camptothecin **240**,[104] and chaboside **241**.[105] Although lurtotecan was first prepared using Friedlander condensation approach, the more efficient synthesis based on the Comins approach was used to prepare a large quantity of the compound.

5. The Michael addition approach (D ring construction)

Both intermolecular and intramolecular Michael reactions have been applied to construction of the pyridone D-ring of

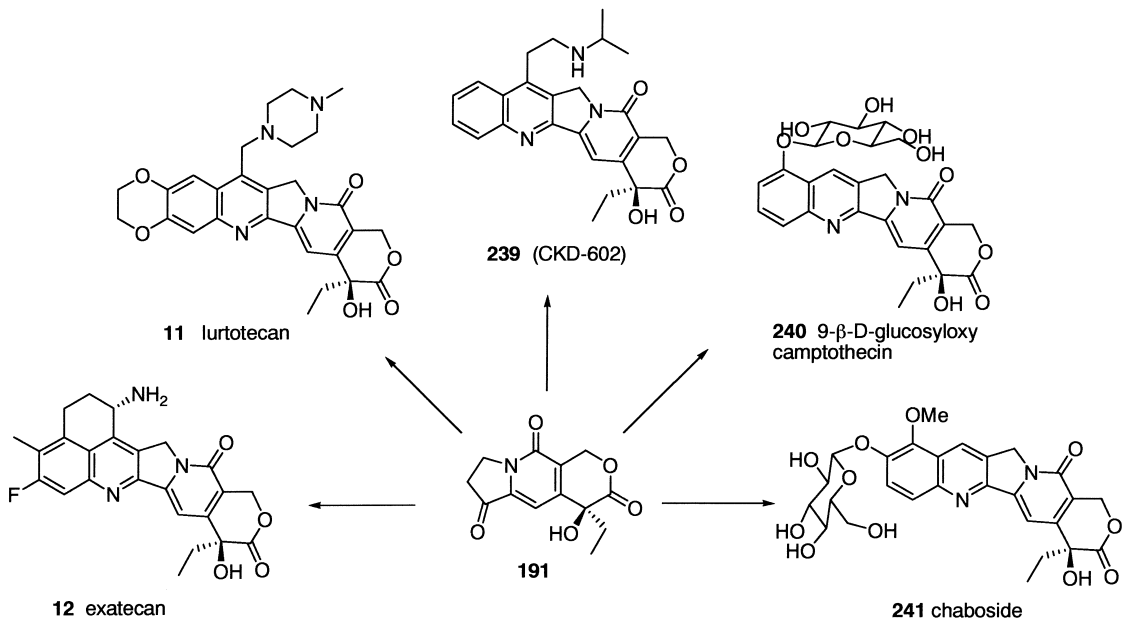
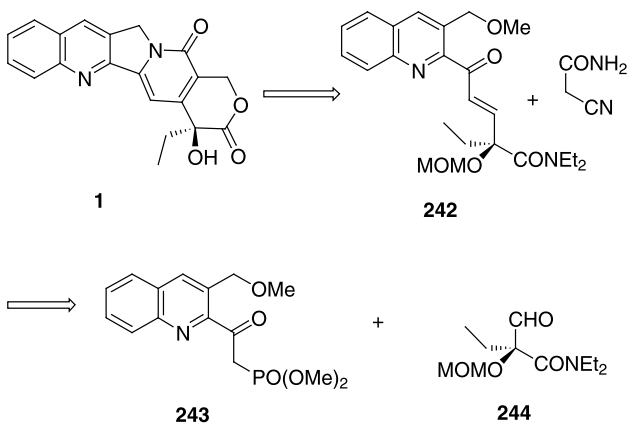


Figure 10. Drug candidates and natural products prepared by the Friedlander condensation.



Scheme 48.

camptothecin. These reactions are featured in the total syntheses of (*S*)-camptothecin reported by the Ciufolini group, (±)-camptothecin by the Chavan group and mappicine ketone by the Greene group.

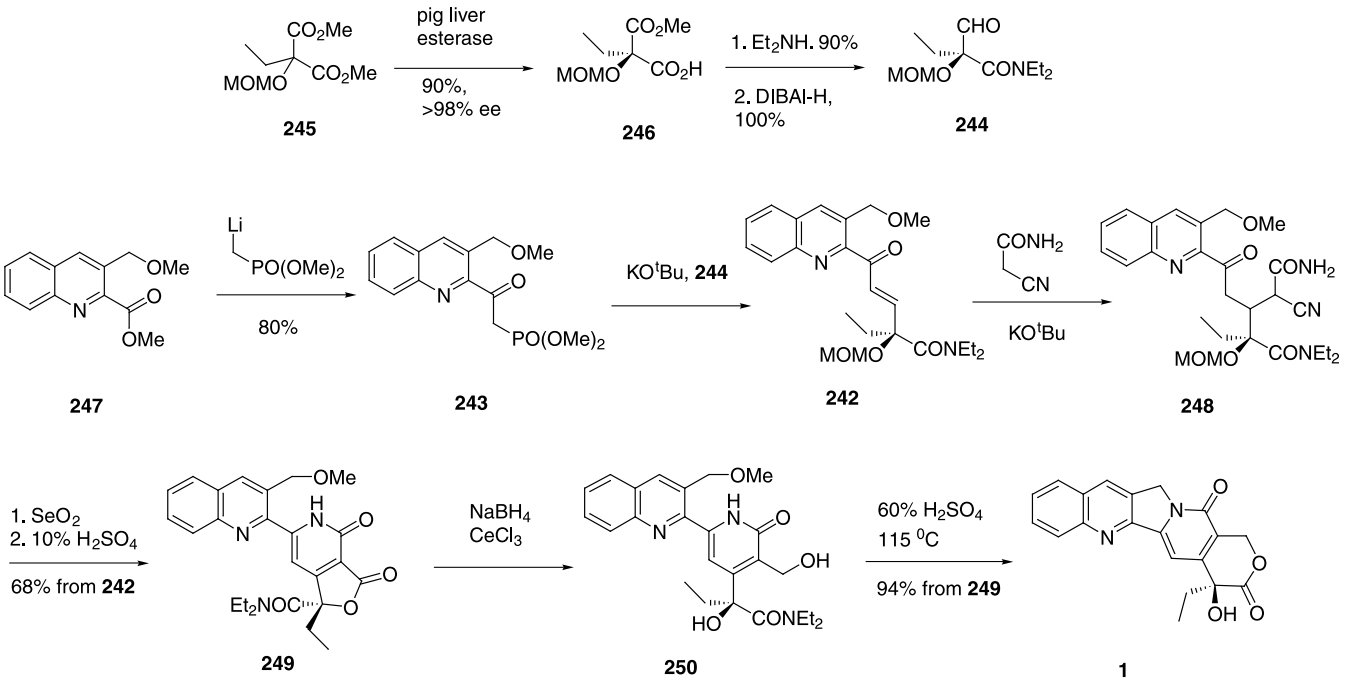
5.1. Ciufolini's total synthesis of (+)-camptothecin: intermolecular Michael addition

The retrosynthetic analysis by the Ciufolini group's intermolecular Michael addition approach is shown in Scheme 48.[106–108] This approach used α,β-unsaturated ketone **242** as a Michael addition acceptor and this intermediate could be derived from Horner–Emmons reaction of **243** and aldehyde **244**, which has the required stereocenter for camptothecin.

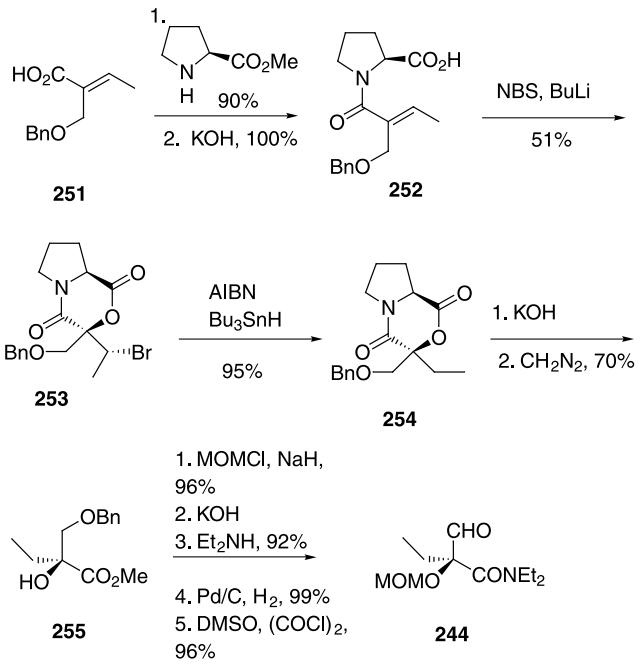
Ciufolini's synthesis of camptothecin is shown in Scheme 49. The chiral aldehyde **244** was made starting with enzymatic desymmetrization of a malonate **245** using pig liver esterase. This procedure yielded acid **246** in 90% yield and >98% ee. The acid was then converted to a diethyl amide, which was then reduced with DIBAL-H to give aldehyde **244**. Phosphate **243** was prepared from ester **247** in 80% yield. Condensation of **243** with aldehyde **244** gave enone **242**. Intermolecular Michael addition of the potassium enolate of 2-cyanoacetamide to enone **242** gave **248** ready for pyridone formation. Treatment of **248** with SeO_2 and ^tBuOOH effected the formation of pyridone and subsequent treatment with acid effected lactonization to give a pyridone lactone **249**. The lactone was then reduced to give an alcohol **250**. The final treatment of **250** with 60% H_2SO_4 in ethanol at 115°C effected formation both E-ring and C-ring to give (20*S*)-camptothecin in 94% yield for 2 steps.

An alternative synthesis of the key intermediate aldehyde **244** was reported by Jew, Park and co-workers using an asymmetric bromolactonization.[109] This synthesis is shown in Scheme 50. Acid **251** was prepared from a 1,3-dihydroxy acetone over 7 steps. It was coupled with proline methyl ester and the product was hydrolyzed to give acid **252**. The proline moiety now functions as a chiral auxiliary. Upon treatment with NBS and BuLi, bromolactonization yielded lactone **253** in 51% yield with >99% de. The bromide was then reduced with Bu_3SnH. Hydrolysis of **254** followed by methyl ester formation gave ester **255**, which was then converted to aldehyde **244** over 5 steps. This route converts **251** to aldehyde **244** in 11 steps with 25% overall yield and >99% ee.

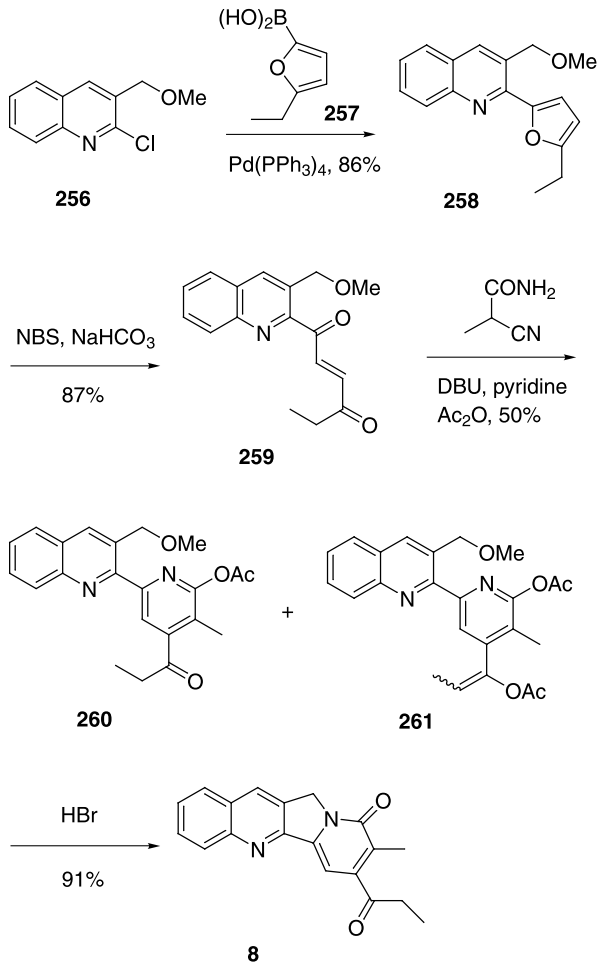
The Ciufolini group recently reported a synthesis of mappicine ketone using the same strategy (Scheme 51).[110] Suzuki coupling of chloroquinoline **256** with furan boronic acid **257** gave furan **258**. Then the furan ring was oxidatively cleaved to give enone **259** in 87% yield. Reaction of enone **259** with 2-methylcyanoacetamide under modified DBU/pyridine/Ac_2O conditions gave a



Scheme 49.



Scheme 50.

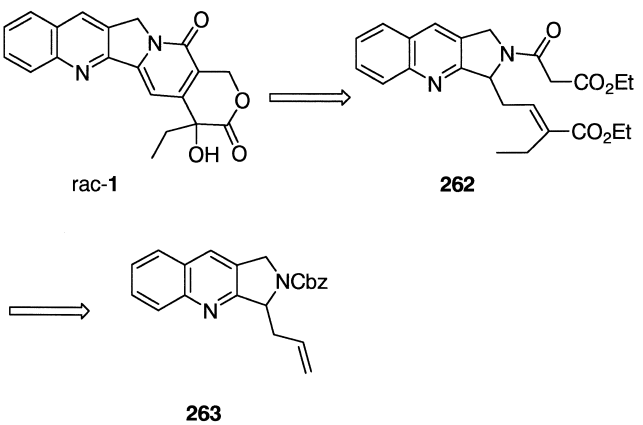


Scheme 51.

mixture of pyridines **260** and **261** in 50% yield. Treatment of the pyridines with HBr yielded mappicine ketone **8** in 91% yield.

5.2. Chavan's total synthesis of (±)-camptothecin: intramolecular Michael addition

The Chavan groups' retrosynthetic analysis of camptothecin is based on an intramolecular Michael reaction.[111] As shown in Scheme 52, the pyridone D-ring could be derived from an α,β-unsaturated ester **262**, which could be derived from alkene **263**.



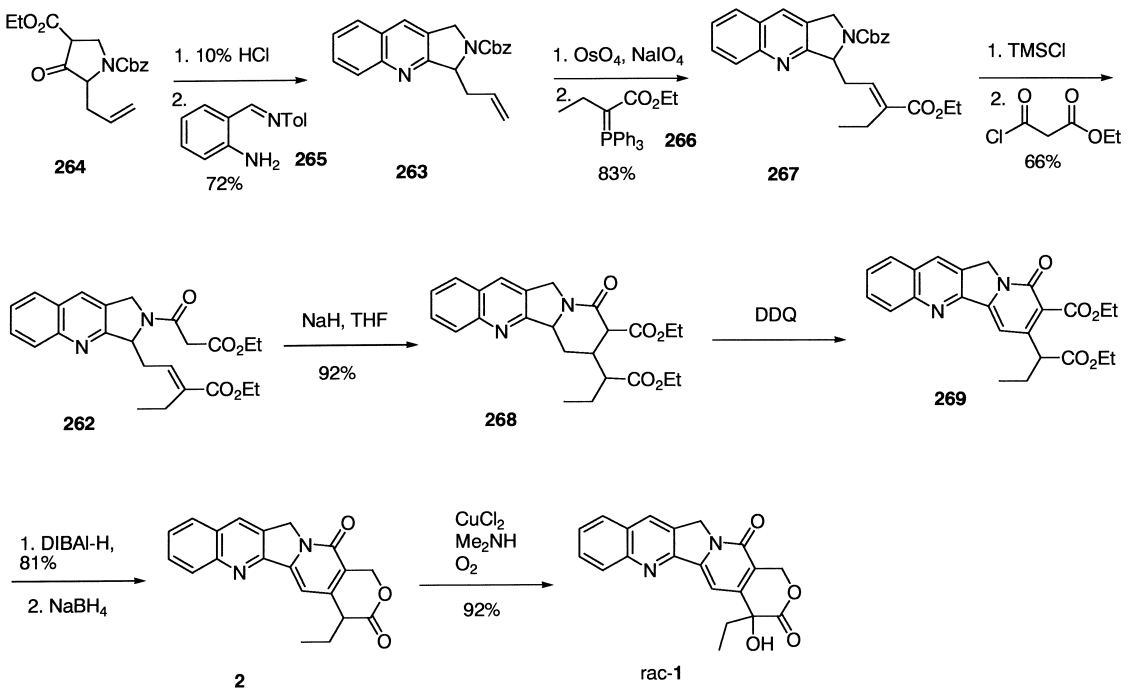
Scheme 52.

Chavan's synthesis of racemic camptothecin is shown in Scheme 53. Ketone **264** was prepared from glycine over 4 steps. Hydrolysis and decarboxylation of **264** in HCl gave a ketone intermediate that then underwent a Friedlander condensation with aniline **265** to give quinoline **263**. Oxidative cleavage of the double bond in **263** resulted in an aldehyde. Subsequent Wittig reaction with phosphonium salt **266** gave α,β-unsaturated ester **267**. The Cbz protective group was removed and the resulting amine was acylated to give amide **262**. Upon treatment with NaH, amide **262** underwent intramolecular Michael addition to give cyclic amide **268** in 92% yield. DDQ oxidation furnished the pyridone D-ring to give diester **269**. The benzoyl ester was selectively reduced by using DIBAL-H in the presence of aliphatic ester to give an aldehyde, which was further reduced and lactonized to give 20-deoxycamptothecin **2**. Hydroxylation of **2** using Danishefsky's conditions yielded racemic camptothecin in 92% yield.

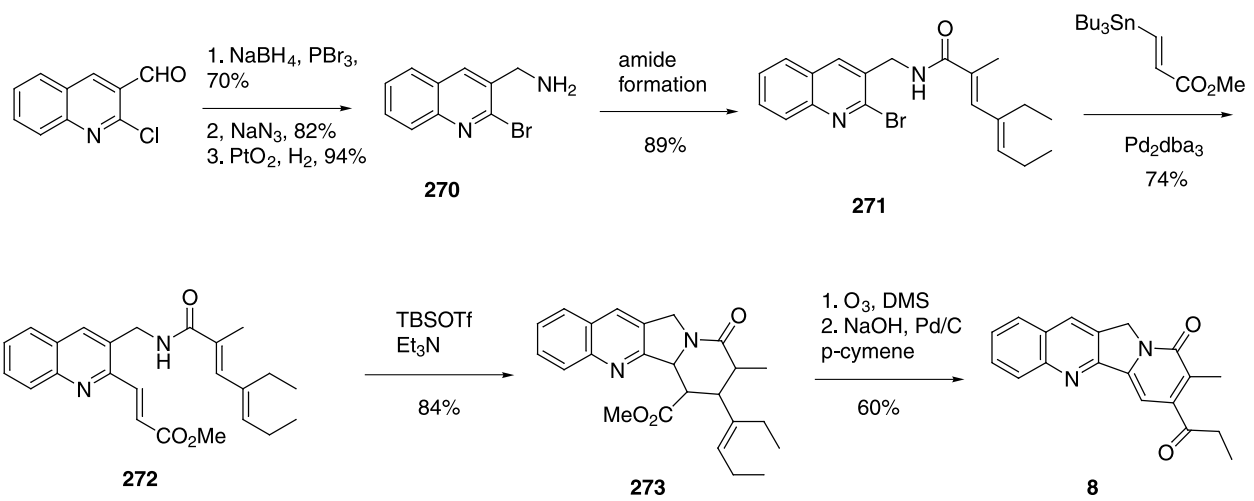
5.3. Greene's total synthesis of mappicine ketone: double Michael addition

Greene and co-workers reported an approach towards the polycyclic quinoline structure through simultaneous construction of both the CD rings using a double Michael addition reaction.[112] This approach was demonstrated by synthesis of mappicine ketone shown in Scheme 54.

Amine **270** was prepared from 2-chloro-3-formyl quinoline over 3 steps. This was then converted to amide **271**. Subsequent Stille reaction with methyl 3-stannyl acrylate furnished quinoline **272**. Treatment of **272** with TBSOTf and Et_3N gave tetracycle **273** in 84% yield by a double Michael addition. In addition to the preferred double Michael reaction mechanism, a Diels–Alder reaction of the resulting silyl imino ether may also be possible. Ozonolysis of **273** furnished a ketone. The final aromatization,



Scheme 53.



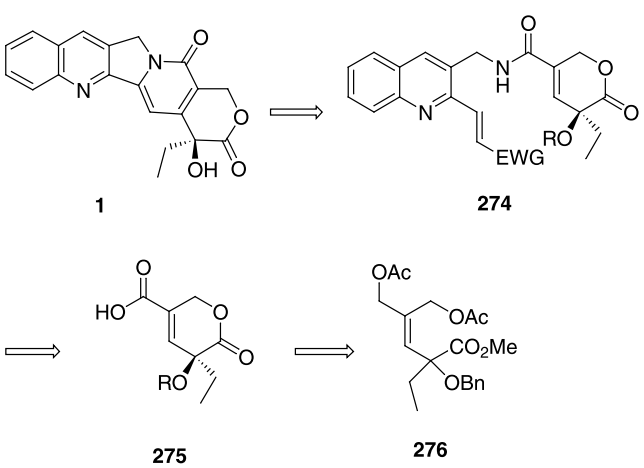
Scheme 54.

hydrolysis and decarboxylation were accomplished by a one-step procedure to yield mappicine ketone **8** in 60% yield.

The same strategy may be applied to synthesis of camptothecin. The substrate for the double Michael addition would be lactone **274**, which could be prepared by acylation of **270** with acid **275**. The Greene group recently reported a synthesis of **275** in 98% ee by enzymatic resolution of diacetate **276**.[113] Thus, the ground work for this approach is in place (Scheme 55).

6. The Diels–Alder reaction approach (B, C and D rings construction)

A six-membered ring is often the target of a [4+2]

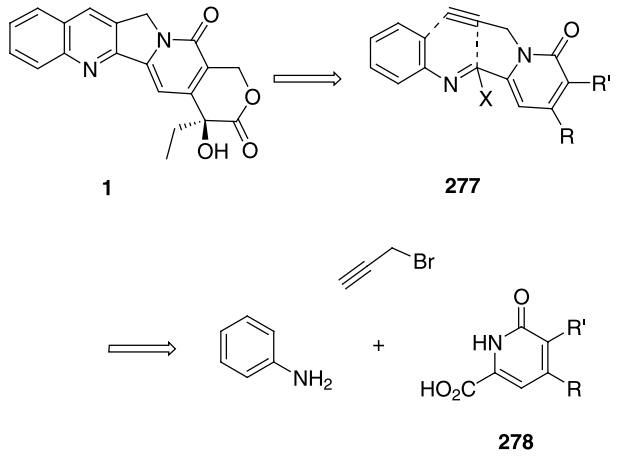


Scheme 55.

cycloaddition reaction. The pyridine B ring and pyridone D ring of camptothecin are of no exception. The successful applications of this strategy include Fortunak's intramolecular hetero-Diels–Alder approach and Boger's intermolecular reverse electron demand hetero-Diels–Alder approach.

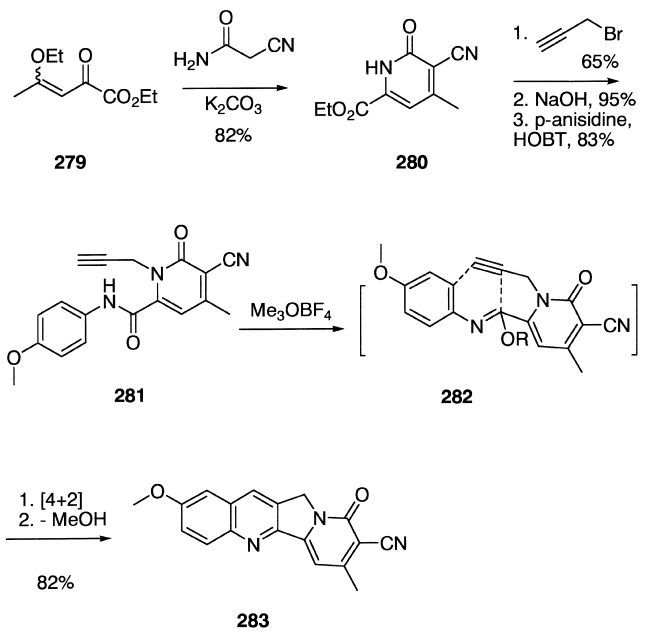
6.1. SmithKline Beecham's total synthesis of topotecan

Fortunak and co-workers in SmithKline Beecham developed a hetero-Diels–Alder strategy to construct the BC rings of camptothecin.[114] The retrosynthetic analysis is shown in Scheme 56. The key reaction is an intramolecular [4+2] cycloaddition of an unactivated alkyne and an aryl imidate **277**, which can be prepared from aniline, propargyl bromide and pyridone acid **278**.

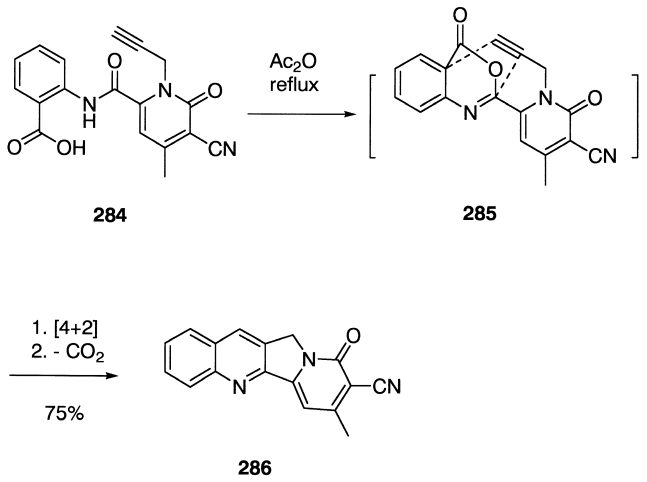


Scheme 56.

This strategy was first demonstrated by a formal synthesis of camptothecin,[114] as shown in Schemes 57 and 58. Pyridone **280** was prepared by a Michael addition of cyanoacetamide to ester **279**. Propargylation of **280** followed by hydrolysis and amide formation yielded amide **281**. Treatment of **281**



Scheme 57.



Scheme 58.

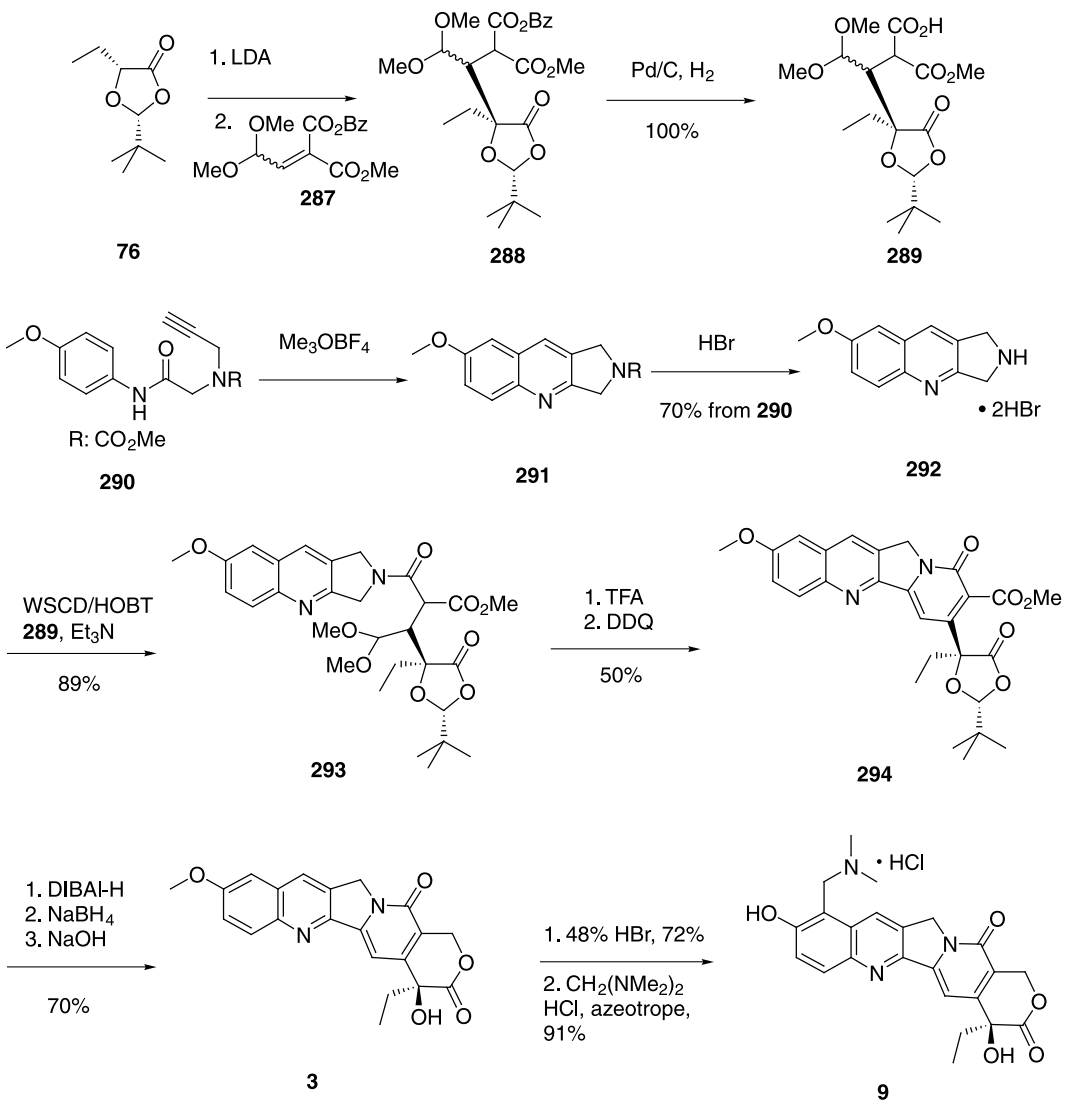
with Me_3OBF_4 effected formation of a *O*-methyl imidate intermediate **282**, which then underwent [4+2] cycloaddition with the 'electron-neutral' alkyne and subsequent elimination of MeOH to give a polycyclic quinoline **283** in 82% yield. This was believed to be the first report of *N*-arylimidates serving as 4π component in a Diels–Alder reaction. The yield of this reaction depends on the substitution pattern on the aromatic ring and the stability of the corresponding imidate. Good yields were obtained for substrates with electron-donating substituents.

A solution for substrates without electron-donating group is shown in Scheme 58. The alternative uses substrate **284**. Refluxing **284** in acetic anhydride resulted in a benzoxazinone **285**, which underwent cycloaddition and elimination of a CO_2 to give polycyclic quinoline **286** in 75% yield. The conversions of **283** and **286** to racemic 10-methoxycamptothecin and camptothecin are known.[115]

Fortunak's asymmetric synthesis of anticancer drug topotecan by using above [4+2] cycloaddition strategy is shown in Scheme 59.[116] Enolate formation of **76** followed by addition to Michael acceptor **287** provided compound **288** as a mixture of diastereomers. Hydrogenolysis yielded acid **289**. Amide **290** was prepared from bromoacetyl bromide over 2 steps. Similar to the Diels–Alder reaction in Scheme 57, aryl amide **290** was treated with Me_3OBF_4 to give a quinoline **291**, which was deprotected with HBr to give amine **292** in 70% yield for 2 steps. Subsequent coupling with acid **289** gave amide **293**. Treatment of **293** with TFA followed by DDQ oxidation effected formation of the pyridone ring to give **294** in 50% yield. Then the ester group was reduced and subsequent lactonization yielded 10-methoxycamptothecin **3** in 70% yield. The methyl ether was cleaved with HBr to give 10-hydroxycamptothecin, which then underwent a Mannich reaction to give topotecan **9** in 91% yield and >99.5% ee.

6.2. Boger's total synthesis of (−)-mappicine and (+)-camptothecin

Boger and co-workers developed a room temperature, inverse electron demand Diels–Alder reaction of a *N*-methylsulfonyl-1-aza-1,3-butadiene and applied it to asymmetric synthesis

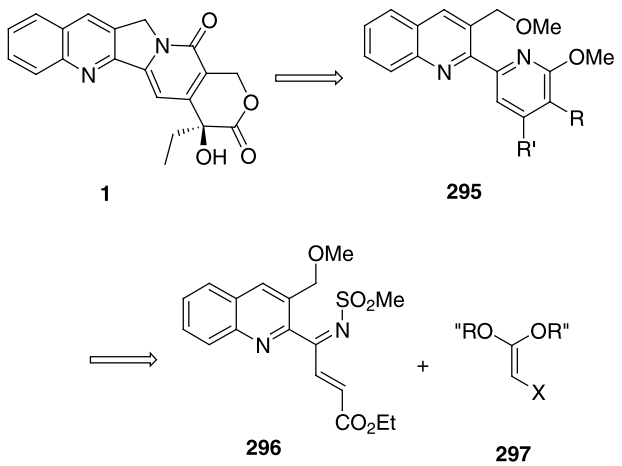


Scheme 59.

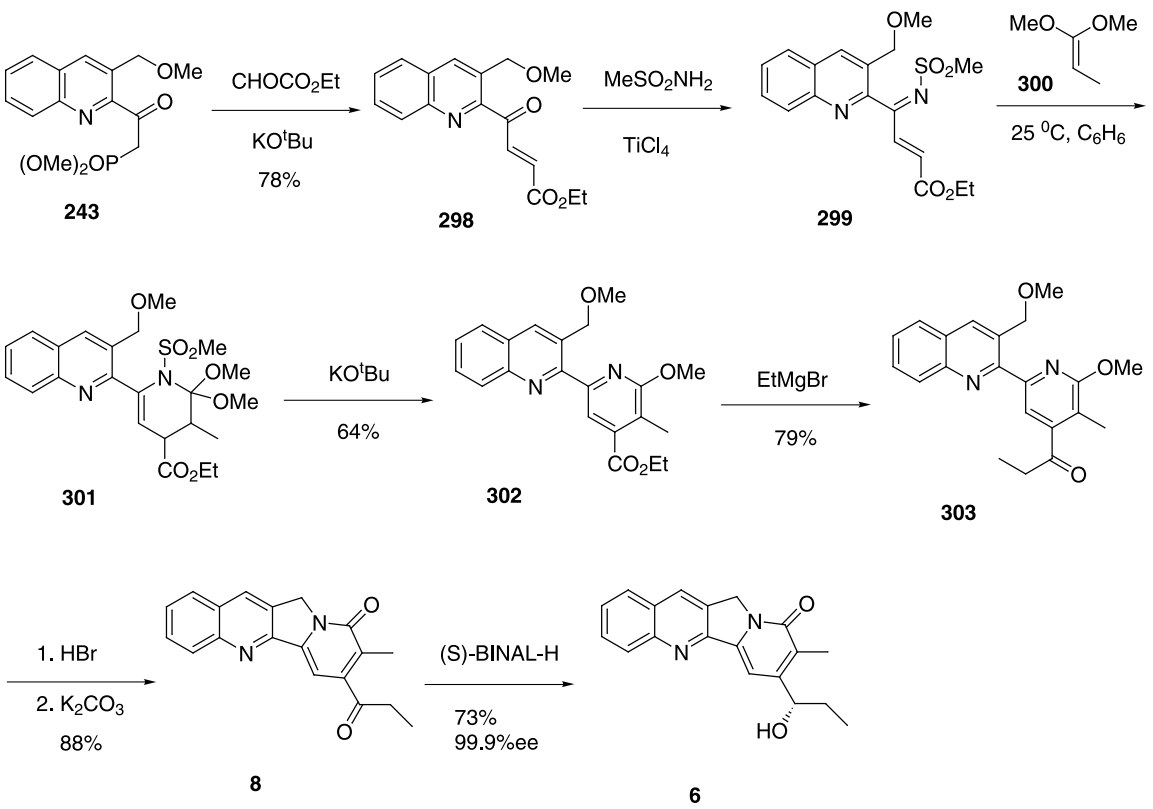
of both mappicine[117] and camptothecin.[118] In these syntheses, the Diels–Alder reaction was used to construct the pyridone D ring of these polycyclic quinoline alkaloids. As shown in their retrosynthetic analysis (Scheme 60), camptothecin can be derived from pyridine **295**, which in turn can be obtained by Diels–Alder reaction between an electron poor 1-aza-1,3-diene **296** and an electron-rich dienophile **297**.

The strategy shown in Scheme 60 was first demonstrated in a total synthesis of mappicine.[117] Phosponate **243** was first prepared from 2-formyl aniline over 5 steps. This intermediate was also used in Ciufolini's synthesis of camptothecin. Wadsworth–Horner–Emmons reaction of **243** with ethyl glyoxylate yielded enone **298**, which was then condensed with methanesulfonamide in the presence of $TiCl_4$ to give *N*-sulfonyl-1-aza-1,3-butadiene **299**. The inverse electron demand Diels–Alder reaction of **299** with electron-rich olefin **300** proceeded at room temperature to give a [4+2] cycloadduct **301**, which was then aromatized to pyridine **302** in 65% overall yield by treatment of ^{t}BuOK. Addition of EtMgBr to ester **302** yielded ethyl ketone **303**, which was then treated with HBr to give mappicine ketone **8** in 88% yield. Reduction of **8** with (*S*)-BINAL-H gave mappicine **6** in 73% yield and 99.9% ee (Scheme 61).

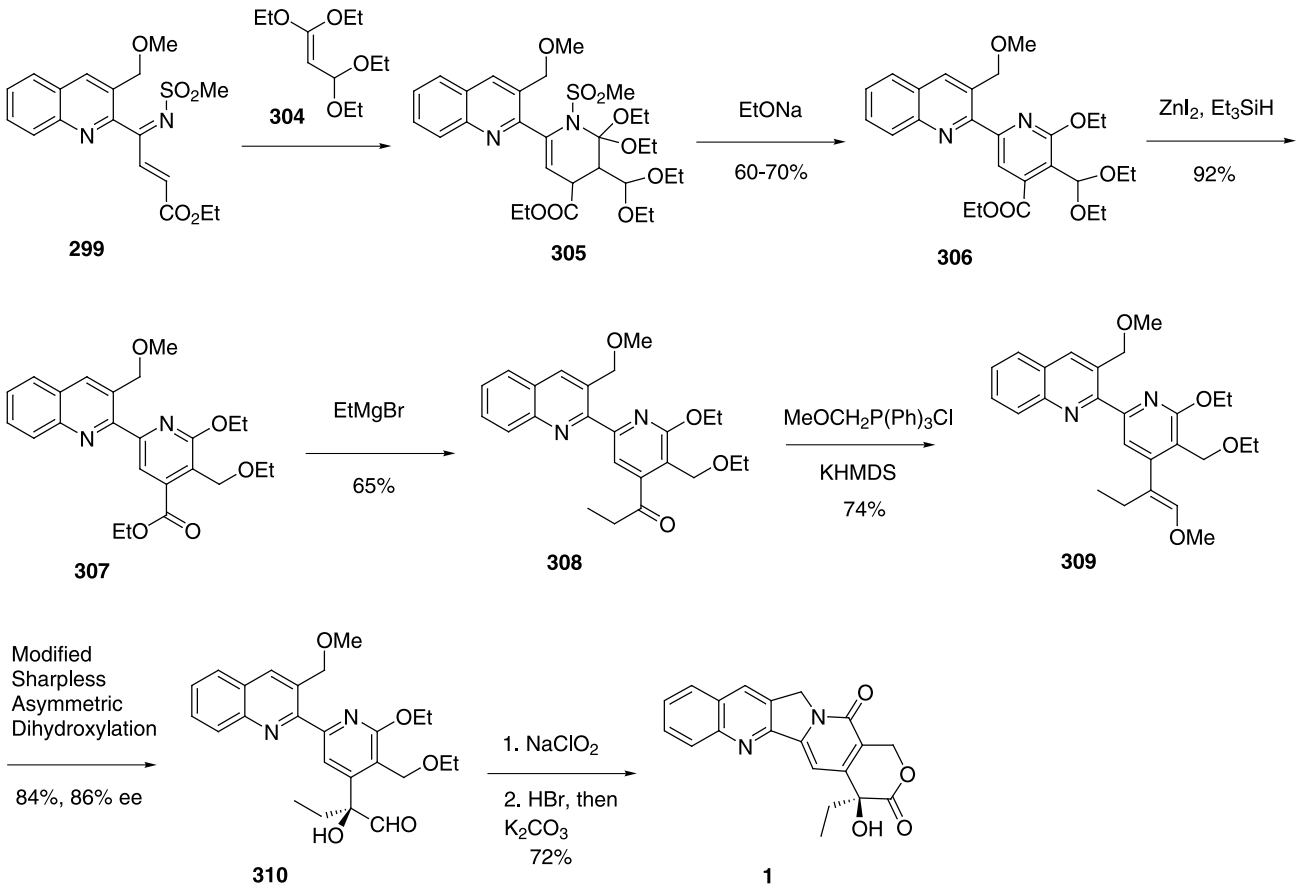
The same strategy was recently applied to an asymmetric total synthesis of camptothecin.[118] Inverse electron demand



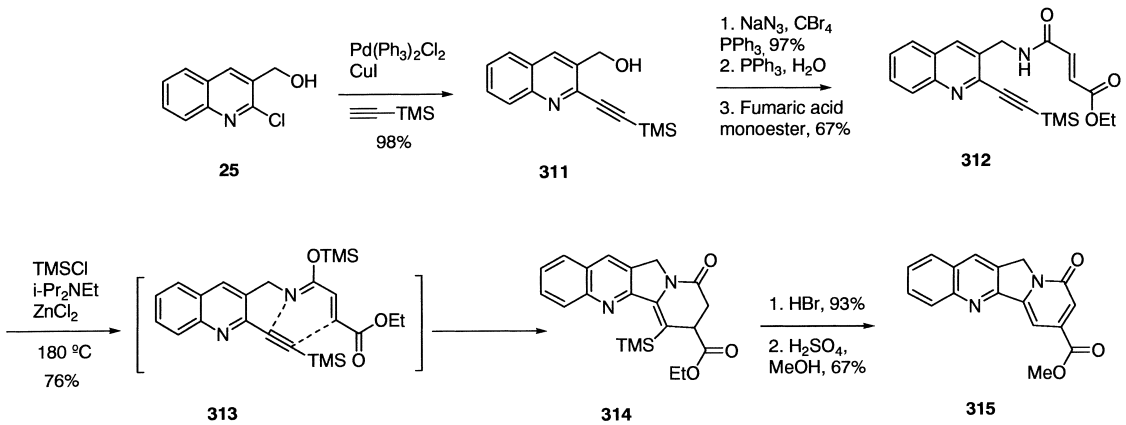
Scheme 60.



Scheme 61.



Scheme 62.



Scheme 63.

Diels–Alder reaction of **299** with electron-rich olefin **304** proceeded at room temperature and gave [4+2] cycloadduct **305**, which was then treated with NaOEt to give pyridine **306** in 60–70% yield. The diethyl acetal **306** was reduced under ZnI_2/Et_3SiH conditions to give an ethyl ether **307** in high yield. Reaction of **307** with EtMgBr gave ethyl ketone **308**, which underwent a Wittig reaction to give vinyl methyl ether **309** in 74% yield. Sharpless asymmetric dihydroxylation of the *trans*-vinyl ether **309** provided a α-hydroxy aldehyde **310** in 84% yield and 86% ee. The aldehyde was oxidized to an acid, and subsequent treatment with HBr followed by K_2CO_3 effected C, E rings closure to give (*S*)-camptothecin in 72% yield (Scheme 62).

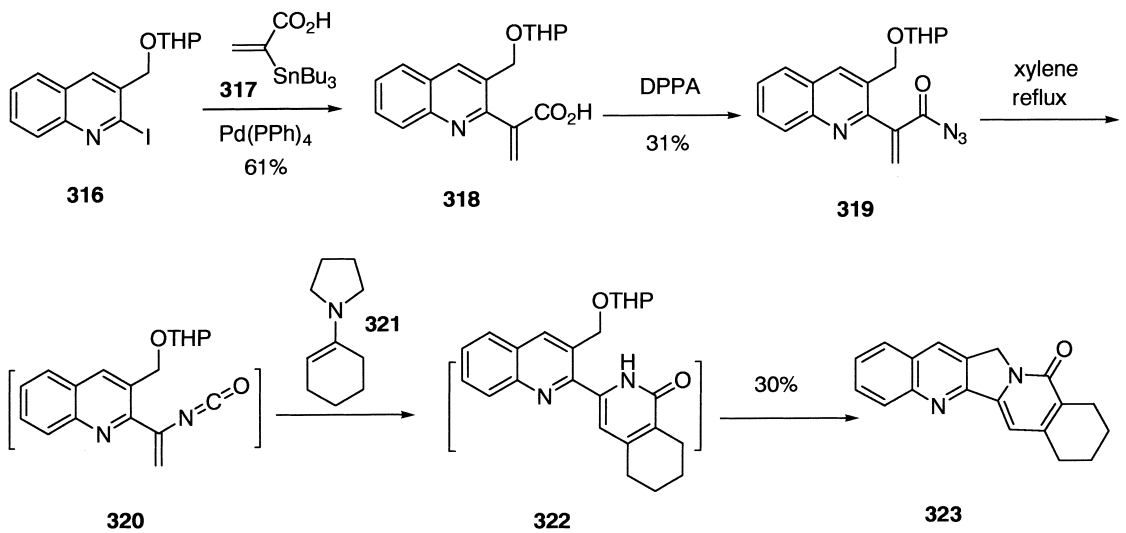
6.3. Other Diels–Alder approaches

Toyota, Ihara and co-workers reported a formal synthesis of mappicine by construction of the CD rings using an intramolecular Diels–Alder reaction.[119,120] Their synthesis is shown in Scheme 63. Sonogashira reaction of quinoline **25** provided alkyne **311**, which was then converted to amide **312** after hydoxy-amine conversion and coupling with fumaric acid monoethyl ester. Heating **312** with TMSCl, base and $ZnCl_2$ in a sealed tube at 180°C effected a hetero-Diels–Alder reaction through intermediate **313** to give the [4+2] cycloadduct **314** in 76% yield. Elimination of TMS group by treatment with HBr followed by autoxidation promoted by the electron-withdrawing ethyl ester group gave a pyridone product. Subsequent ester exchange reaction gave quinoline **315** whose conversion to mappicine is known.

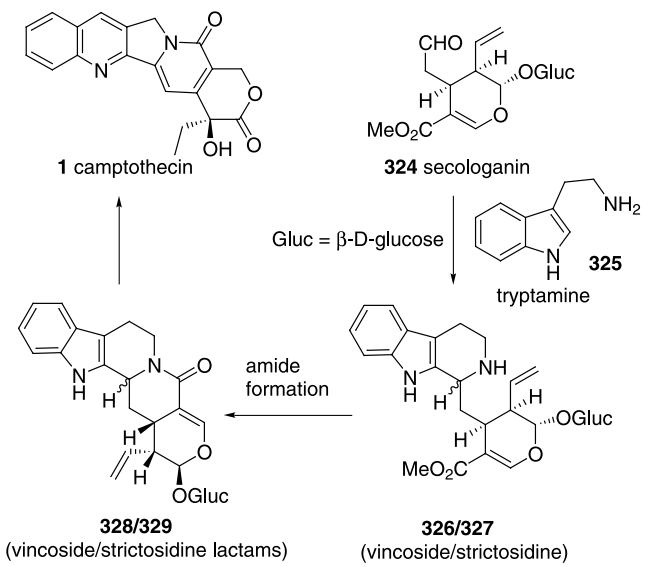
Rigby group reported a synthesis of a camptothecin model by a [4+2] cycloaddition of vinyl isocyanate (Scheme 64).[121] Quinoline **316** was prepared from acetanilide over 2 steps. Stille reaction of **316** with stannyl acid **317** yielded acid **318** in 61% yield. Acid **318** was then converted to acyl azide **319**, which then underwent a Curtius rearrangement when refluxed in xylene to give a vinyl isocyanate intermediate **320**. A [4+2] cycloaddition with enamine **321** proceeded to give a Diels–Alder product **322**, which was simultaneously converted to camptothecin model **323** under the reaction conditions in 30% overall yield.

7. Biomimetic synthesis of (±)-camptothecin

Early speculation on the biogenesis of camptothecin (Scheme 65) proposed that camptothecin is derived from



Scheme 64.



Scheme 65.

vincoside/strictosidine lactams **328/329**, because of the known readily conversion of indole to quinoline and the skeletal similarity between **1** and **328/329**. Thus, camptothecin belongs to the monoterpenoid indole alkaloid family. Lactams **328/329** are derived from vincoside/strictosidine **326/327**, which can be synthesized by condensation of secologanin **324** with tryptamine **325**. This biogenetic speculation was confirmed by incorporation of labelled strictosidine lactam into camptothecin. However, little is known about the detail of this process. Recently, Brown and co-workers reported a biogenetically patterned synthesis of racemic camptothecin from strictosidine lactam.[122]

The Brown group's synthesis is shown in Scheme 66. Strictosidine lactam **329** was treated with acetic anhydride to give a tetraacetate of **329**, which was then treated with $NaIO_4$ to cleave the indole ring and gave a lactam product **330** in 64% yield. Heating **330** with Et_3N in methanol gave an aldol condensation product quinolone **331** in 78% yield, which was then treated with $SOCl_2$ to give a chloroquinoline **332**. Subsequent Ni-catalyzed hydrogenation of **332** not only reduced the two C–C double bonds in **332**, but also partially reduced the quinoline to give a dihydroquinoline **333** in 89% yield. Oxidation of **333** with DDQ yielded quinoline **334**, which has the aromatic core of camptothecin. The glucose moiety in **334** was removed by sequential treatment with NaOMe and β-glucosidase to give lactol **75** in 50% yield. The lactol was oxidized with PCC to give 20-deoxycamptothecin **2**, which was further oxidized with O_2 and $CuCl_2$ in DMF to give racemic camptothecin in 60% yield.

The Aimi group also reported a similar synthetic sequence, which was applied to synthesis of two newly isolated camptothecinoids **335** (OPHR-17) and **336** (OPHR-23, Fig. 11) starting from tryptamine and secologanin.[123]

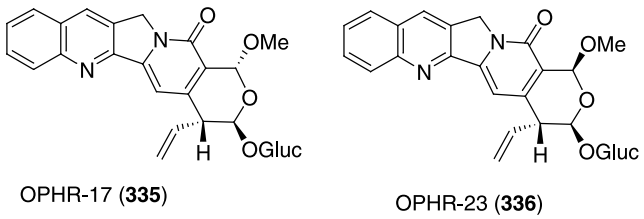
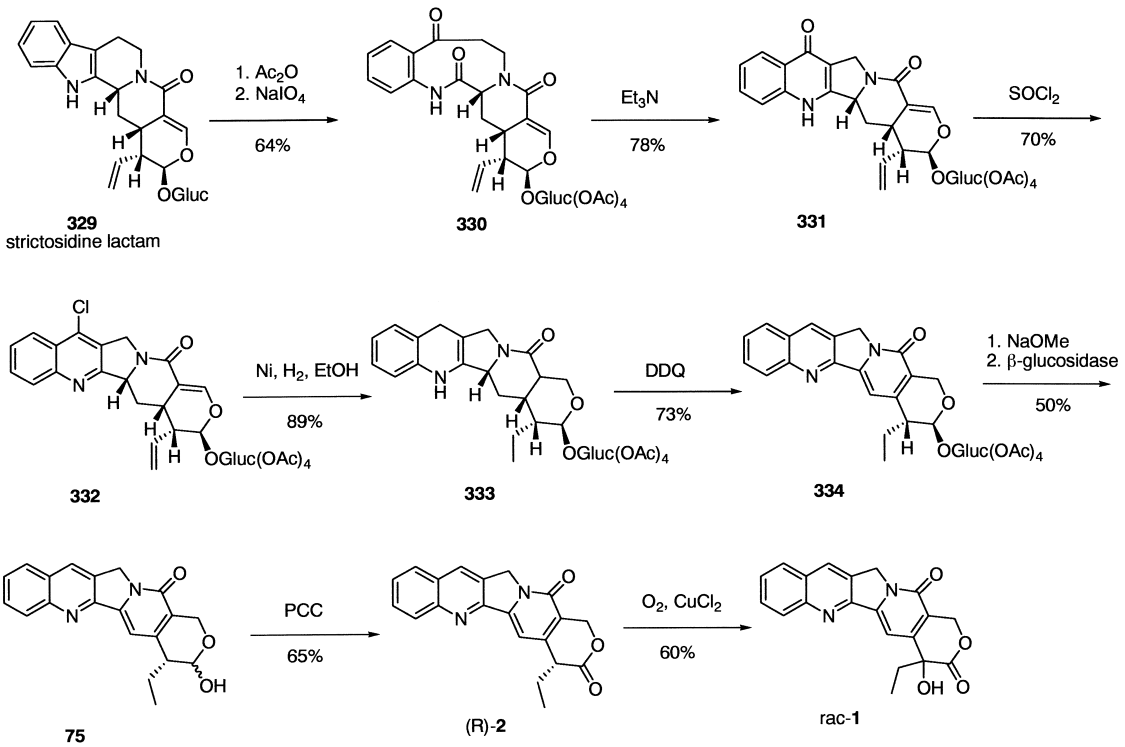


Figure 11.

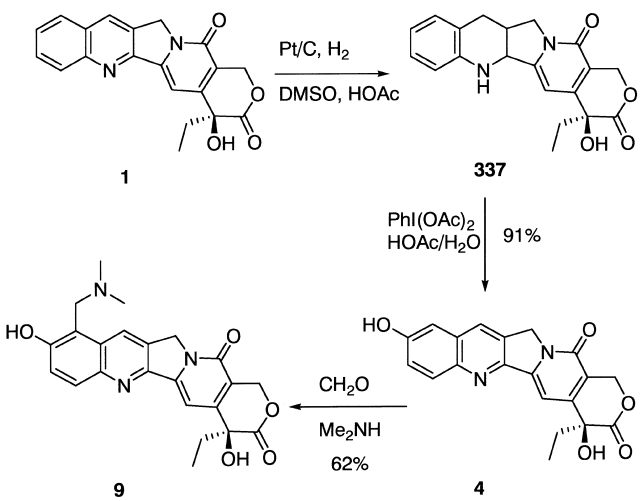


Scheme 66.

8. Semi-synthesis of anti-cancer drugs and drug candidates of camptothecin family

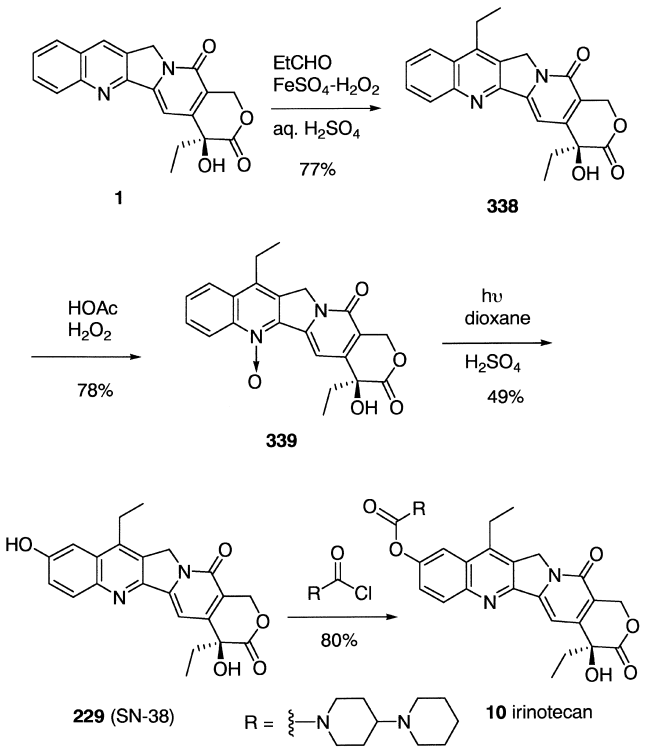
Camptothecin can be isolated from various sources in large quantity and is commercially available. This makes semi-synthesis of camptothecin drug candidates very attractive for it provides shorter synthetic route and higher overall yield comparing to total synthesis. The chemical modification of camptothecin has been extensively studied and resulted in A, B, C, D, E ring analogs of camptothecin. While more complex analogs still rely on total synthesis, anticancer drugs topotecan, irinotecan and a number of drug candidates have been prepared by semi-synthesis, and are summarized here.

The semi-synthesis of topotecan is shown in Scheme 67. A reduction–oxidation sequence converts camptothecin to 10-hydroxycamptotehcin **4**. The most practical conditions for this process were developed in SmithKline Beecham.[124] Platinum-catalyzed hydrogenation of camptothecin gave tetrahydroquinoline **337**, which was oxidized with $PhI(OAc)_2$ in one pot to give 10-hydroxycamptothecin **4** in excellent yield. Condensation of **4** with formaldehyde and dimethyl amine yielded topotecan **9** in 62% yield.[125]



Scheme 67.

The Sawada group applied the Minisci type reaction to camptothecin and it turned out to be very fruitful. The Minisci reaction features carbon radical addition to electron deficient heteroaromatics such as pyridine and quinolines. A variety of 7-substituents of camptothecin were introduced by this approach. The semi-synthesis of irinotecan by the Sawada group is shown in Scheme 68[126,127] Reaction of propanal in the presence of $FeSO_4$, H_2O_2 in aqueous acidic medium generates an ethyl radical, which adds to the 7-position of camptothecin to give 7-ethylcamptothecin **338**. Oxidation of **338** to its *N*-oxide **339** followed by photo irradiation in the presence of acid gave the corresponding 7-ethyl-10-hydroxy camptothecin **229** in 49% yield. Also known as SN-38, compound **229** is the actual anticancer drug released in vivo from its prodrug irinotecan. The photo irradiation step required high dilution, thus limiting large-scale preparation using these conditions. Acylation of **229** gave the prodrug irinotecan with about 20% overall yield.

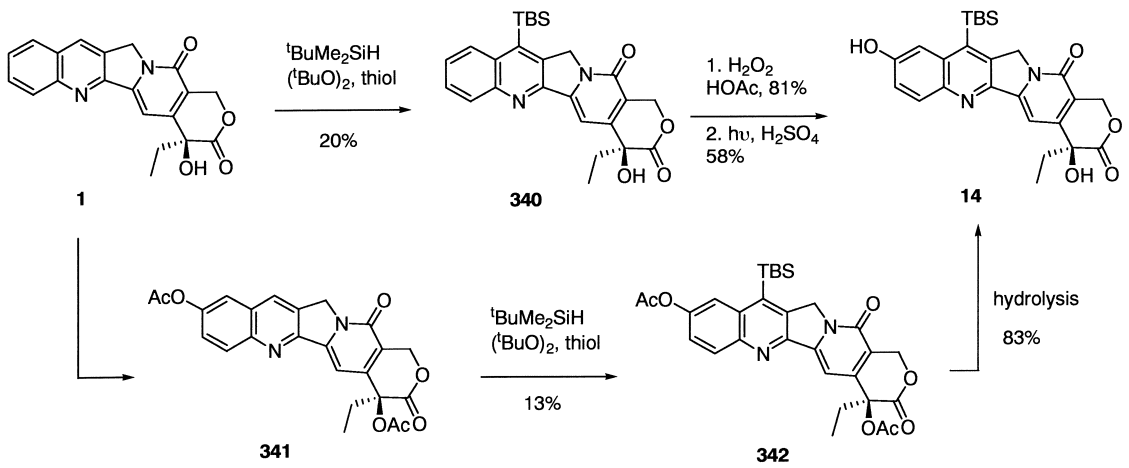


Scheme 68.

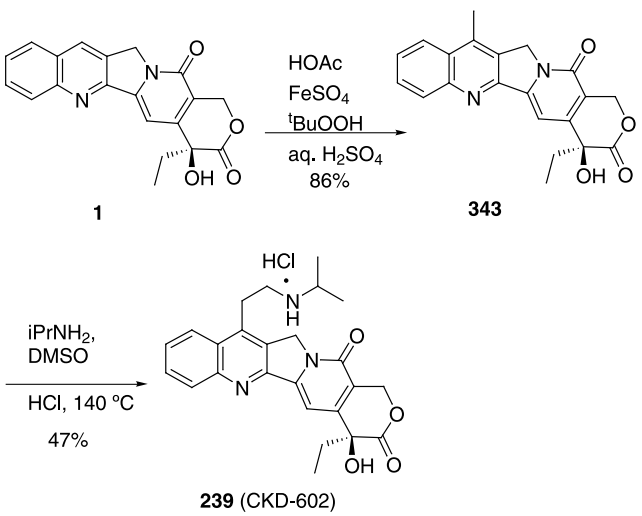
A related silyl radical addition approach was taken by Curran and co-workers to prepare silatecans, especially the drug candidate DB-67.[128] The Curran group discovered that thiol is beneficial in effecting silyl radical addition to camptothecin. Refluxing camptothecin with excess silanes, radical initiator and thiol promoter in dioxane yielded 7-silyl camptothecins in about 20% yield, in addition to 50–60% unreacted camptothecin. Using procedure similar to Sawada's, silatecan **340** was converted to its *N*-oxide and subsequent photo irradiation yielded DB-67 (**14**) in about 10% overall yield for this three-step sequence without counting recycle of unreacted camptothecin. Another route used diacetate **341**. Silyl radical addition followed by hydrolysis, either under acidic conditions or basic conditions, yielded DB-67 as well. The latter route avoided using the impractical photo rearrangement conditions. This study also shows the first example of addition a silyl radical to an electron deficient heteroaromatics (Scheme 69).

The Ahn group developed a semi-synthesis of drug candidate **239**.[129] 7-Methylcamptothecin **343** was prepared from camptotehcin using a Minisci type reaction. Then **343** underwent a Mannich type reaction with $^{i}PrNH_2$ in DMSO to give **239** in 47% yield. In this reaction, DMSO was used as both solvent and a methyl source (Scheme 70).

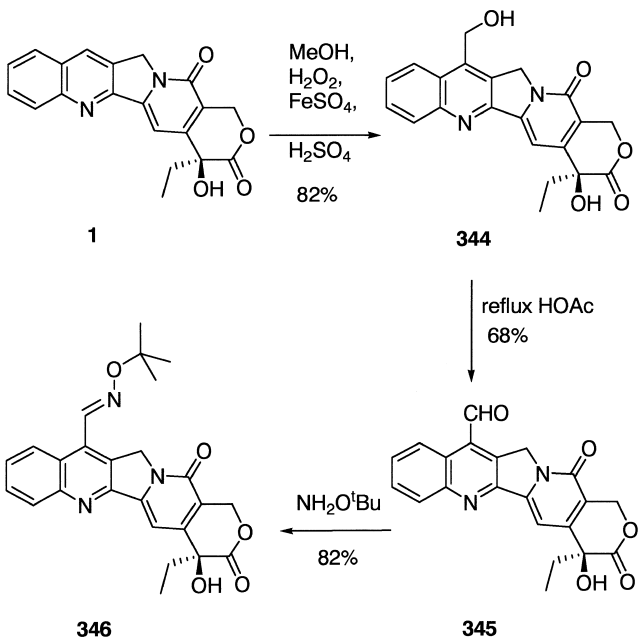
The Sawada group prepared 7-hydroxymethylcamptothecin **344** from camptothecin by running the Minisci type reaction with MeOH as cosolvent.[130] A hydroxymethyl radical was generated under such conditions, and subsequent addition to camptothecin gave **344** in 82% yield. Reflux of **344** in acetic acid yielded 7-formylcamptothecin **345** in 68% yield. Merlini, Zunino and co-workers reacted **345** with *O*-alkylhydroxyamines to give 7-oxyiminomethyl



Scheme 69.



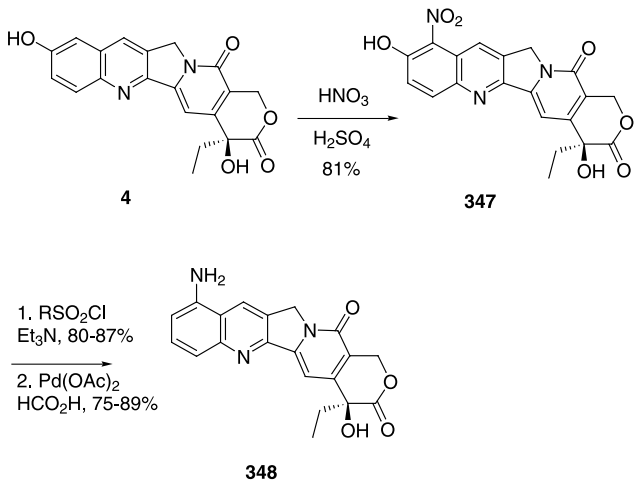
Scheme 70.



Scheme 71.

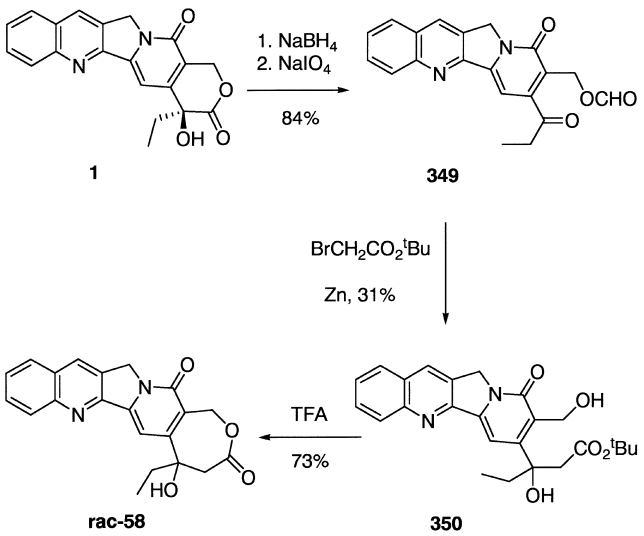
camptothecins including drug candidate **346** (Gimatecan) (Scheme 71).[131]

Nitration reaction is the key reaction in synthesis of drug candidates 9-nitrocamptothecin and 9-aminocamptothecin. Direct nitration of camptothecin gave 9 and 12-nitrocamptothecins with latter as the major product.[132] Under the optimized conditions using $K_2NO_3/TlNO_3$ and H_2SO_4, the reaction gave 70% nitration products in 1:1.4 ratio. The unfavored regioselectivity promoted the Cabri group to develop a more regioselective nitration reaction.[133] 10-Hydroxy group was used as the directing group. Nitration of 10-hydroxycamptothecin **4** yielded 10-hydroxy-9-nitrocamptothecin **347**. Subsequent sulfonylation and palladium-catalyzed reduction yielded 9-aminocamptothecin **348** (Scheme 72).



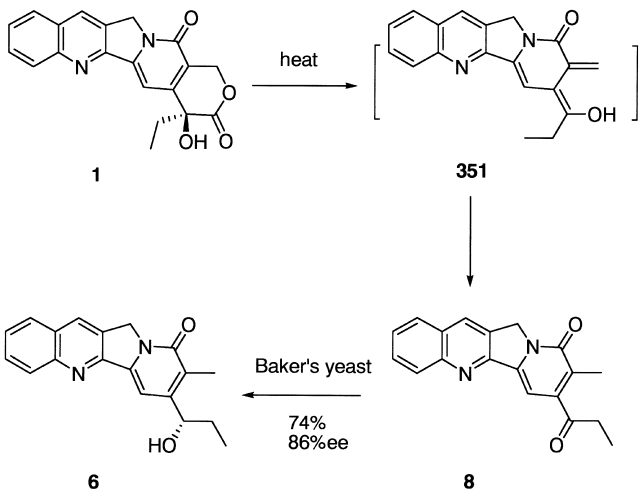
Scheme 72.

Homocamptothecin was first prepared in racemic form by semi-synthesis (Scheme 73).[39] Reduction of camptothecin E-ring lactone gave a lactol. Subsequent oxidation resulted in C–C bond cleavage to give ketone **349**. Reformatsky reaction of **349** furnished β-hydroxy ester **350**, which was converted to racemic homacamptothecin upon treatment with TFA. Semi-synthesis of (+)-homocamptothecin still remains a problem to be solved.



Scheme 73.

Isolation of mappicine ketone in a larger quantity from plant source is difficult because of its low abundance. However, it can be obtained from camptothecin under conditions such as heating with NaN_3,[134] heating (>150°C),[135] microwave irradiation,[136] treatment with Lewis acid ($BF_3{\cdot}Et_2O$),[136] or treatment with silica gel supported $NaHSO_4$.[137] The microwave irradiation appeared to be the best method that gave a clean formation of mappicine ketone with 96% yield in short time (7 min). This degradation goes through a retro-Diels–Alder reaction with elimination of a CO_2 to give an intermediate **351**, which quickly tautomerizes to mappicine ketone **8** by a 1,5-H shift (Scheme 74). Mappicine ketone **8** can be further converted to (*S*)-mappicine **6** in 74% yield and 86% ee by treatment with baker's yeast in buffer solution of pH 7.2.[138] The conversion of camptothecin to mappicine ketone allowed preparation of a number of mappicine ketone analogs from corresponding camptothecin analogs.[135]



Scheme 74.

9. Conclusion and prospectives

It has been an exciting time for natural product camptothecin since the late 1980s and early 1990s. The studies on camptothecin's mechanism of action and discovery of topoisomerase I as a therapeutic target opened a new area for anticancer drug development. Among a tremendous amount of effort in this field are new syntheses of camptothecins, which have been the crucial works that made new anticancer drugs of this family possible.

Summarized in this review are advances on synthesis of camptothecins in last dozen years. Comparing to those first generation of syntheses developed in 1960s and 1970s, the second generation of syntheses are more practical, more efficient and in the most of cases, asymmetric. Some representative new synthetic approaches are Comins's concise total synthesis, Curran's elegant cascade radical annulation strategy, the refurnished Friedlander condensation approach, Ciufolini's Michael addition approach, Fortunak and Boger's novel Diels–Alder strategies. These second generation syntheses and related accomplishments well reflect advances in other fields of modern organic synthesis that have underwent dramatic development in past 10 or 20 years, such as transition metal-catalyzed C–C bond formation, radical chemistry, cascade reactions, new Diels–Alder reactions, asymmetric synthesis, asymmetric catalysis and combinatorial chemistry.

Although camptothecin is always the primary target, the expectation and value of a new synthesis go beyond that. To be applicable to drug discovery, a synthesis needs to be efficient, asymmetric and equally important, use mild conditions. While camptothecin itself is known to be stable under rather harsh conditions, the same may not be true for its analogs. Thus to evaluate a total synthetic route simply by counting the number of steps and the overall yield is not enough. The synthetic studies summarized here have largely accelerated drug discovery in this field. This is evidenced by development of homocamptothecin drug candidates BN80915 (**13**), BN80927 (**68a**) by using Comins type approach, silatecan and homosilatecan drug candidates DB-67 (**14**) and DB-91 (**178**) by using Curran's approach, and drug candidates lurtotecan **11**, exatecan **12** and CKD-602 (**239**) by using the Friedlander condensation approach. Complementary to total synthesis, semi-synthesis remains a unique and important approach in this field leading to anticancer drugs topotecan **9**, irinotecan **10** and drug candidates 9-nitrocamptothecin, 9-aminocamptothecins and gimatecan **346**.

Camptothecin will continue to remain a target for new synthetic methods, which are certainly expected considering the fast development of modern organic synthesis. On the other hand, the continued studies on camptothecin–DNA–topoisomerase I interaction in addition to its detailed mechanism of action may suggest new directions on synthesis of camptothecins. For example, the crystal structure of the ternary complex[10] in conjunction with the success of homocamptothecin brings people's attention to camptothecin E ring. These synthetic routes that construct camptothecin E ring at late stage, such as Boger's synthesis, may show advantages over others on exploration of camptothecin E ring analogs. Those newly developed synthesis may demonstrate their potential in coming years. While interest in camptothecins will remain high for its pharmaceutical potential, so will be the attention on

synthesis of camptothecins. And in turn, the advances on synthesis will continue to contribute to our further understanding of inhibitor–DNA–enzyme interaction and further development of new and better anticancer drugs.

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Biographical sketch

Wu Du received his BS degree in chemistry from the Jilin University in Changchun, China in 1993. After receiving a MS degree from the University of Hawaii working in Professor Richard E. Moore's group on anticancer marine natural product cryptophycin, he joined Professor Dennis P. Curran's group in the University of Pittsburgh in 1998 and then received his PhD in 2002. Under the direction of Professor Curran, he worked on synthesis of anticancer agents of camptothecin family and development of new synthetic method by using a cascade radical cyclization. His PhD work in Pittsburgh contributed to 15 manuscripts and papers in addition to 4 patents and patent applications. He was an Andrew Mellon Fellow of the University of Pittsburgh in 2001 and 2002. Currently, he is a postdoctoral research associate in Professor Dale L. Boger's group in The Scripps Research Institute in San Diego. His research interests include new synthetic methodologies, transition metal-catalyzed reactions, cascade radical reactions, asymmetric catalysis, heterocyclic chemistry, total synthesis of natural product, bioorganic chemistry, medicinal chemistry and drug discovery. His other interests include painting, classic literature, tennis, and Chinese chess, of which he was a twice champion of the Jilin University.