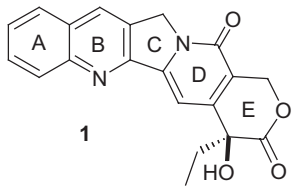
16
Camptothecin and Analogs: Structure and Synthetic Efforts

Sabrina Dallavalle, Lucio Merlini

16.1
Introduction: Structure and Activity

Camptothecin (CPT, **1**) is a natural compound isolated for the first time [1] from the wood of *Camptotheca acuminata* Decne (Nyssaceae), a deciduous plant (xi shu, happy tree) of Southeastern China, but produced also by the Indian Icacinacea *Nothapodytes foetida* (Wight) Sleumer (formerly *Mappia foetida* Miers) [2], and by some other plants [3], the two former being the major sources of the compound.



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Although CPT is not basic, it certainly belongs to the alkaloid family, as its structure clearly shows the derivation from the basic precursors of monoterpenoid indole alkaloids, tryptamine and secologanin. The well-known intermediate of this pathway, strictosamide, has been shown to be a precursor of CPT, by incorporation of a radiolabeled sample [4]. The subsequent steps in the rearrangement of the indole to the quinoline nucleus most probably involve oxidation and recyclization of the C and D rings, oxidation of the D ring and removal of the C-21 glucose moiety, and oxidation of ring E. In agreement with this hypothesis is the isolation of 3-(*S*)- and 3-(*R*) deoxypumiloside and 3-(*S*)-pumiloside from *Ophiorrhiza pumila*, another plant producing CPT. (See ref. [3] for a detailed review of CPT biosynthesis.) (Scheme 16.1). ^{13}C NMR studies have established that the secologanin moiety is formed via the plastidic nonmevalonate (MEP) pathway [5], but details of the last steps of the biosynthesis remain hypothetical.

Camptothecin was discovered during a program of screening plant extracts for antitumor activity, launched by NCI in 1955. The unusual activity of the extracts of *Camptotheca acuminata* against some leukemia cellular lines prompted a study of the

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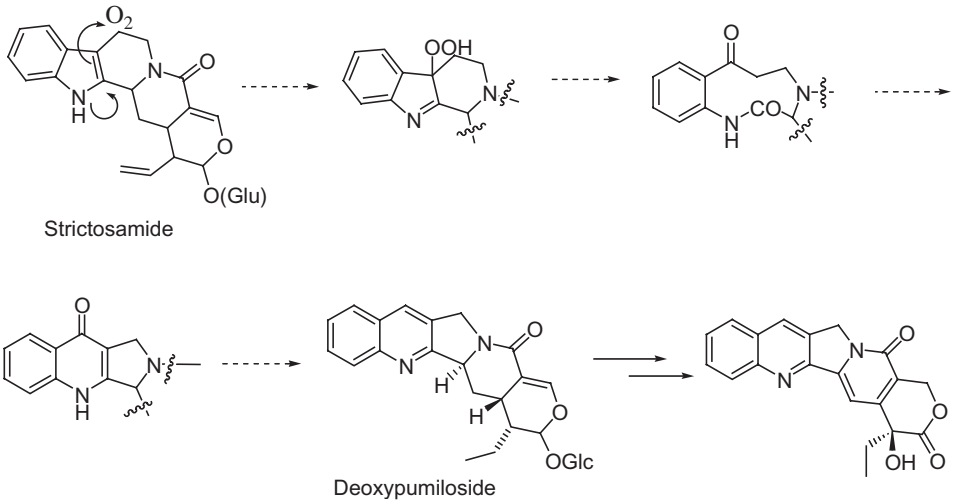
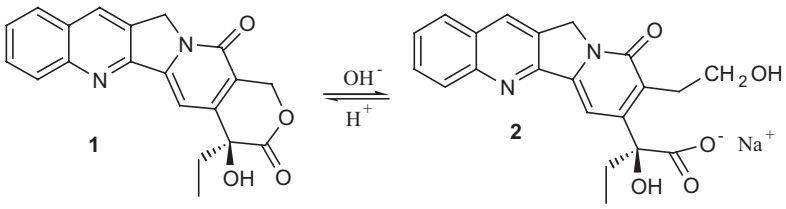


Scheme 16.1 Putative last steps of camptothecin biosynthesis.

components, which led to the bio-guided fractionation, isolation, and structural elucidation of CPT in 1966 [1]. As soon as sufficient material became available, further *in vitro* and *in vivo* assays were conducted, culminating in Phase I and II clinical trials in 1970–1972 [6]. Owing to its extremely low solubility in water, CPT had to be administered as the sodium salt of the hydroxycarboxylic acid **2** (Scheme 16.2). However, shifting of the equilibrium toward the lactone form in tissutal compartments with acid pH caused precipitation of crystals of CPT, which caused severe hemorrhagic cystitis. This effect, together with other toxicities, led to the termination of clinical trials in 1972.

Interest in possible applications of CPT declined. However, renewed interest in CPT emerged when, as a result of a cooperative effort between Johns Hopkins University and SKB, it was found that DNA damage, which is the main reason for the antitumor activity, was due to inhibition of the ubiquitous nuclear enzyme topoisomerase I [7]. Elucidation of the mechanism of action of CPT and, therefore, of a definite biological target at which to aim new drugs gave rise to a fresh wave of research aimed at finding new more active and less toxic camptothecin derivatives.



Scheme 16.2 Lactone—hydroxyacid equilibrium in camptothecin.

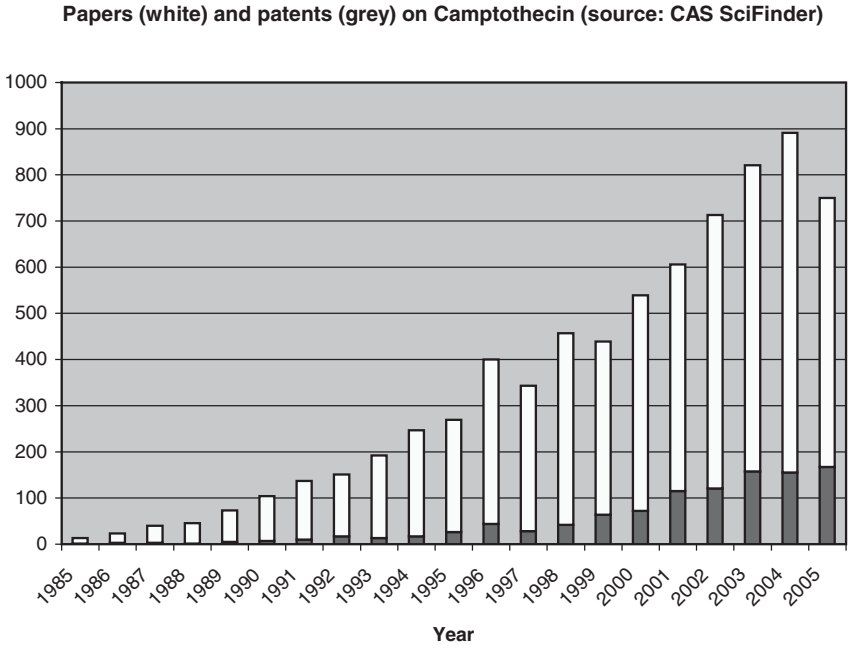


Fig. 16.1 Trend of publications and patents on camptothecins from 1985 to 2005.

This is clearly shown by the sharp increase in the number of publications and patents that followed Liu's paper (Figure 16.1).

To avoid the problems encountered with CPT itself, the introduction of functional groups able to make the compounds sufficiently water soluble to allow intravenous administration was a main issue.

The results of this effort were a detailed pattern of structure–activity relationships (Figure 16.2), and the production of two compounds, topotecan **3**[8] and irinotecan **4**[9], which were approved for clinical use in 1996, the main indications being ovarian and small-cell lung cancer for the former and metastatic colorectal cancer for the latter. Irinotecan is a water-soluble prodrug of the active compound SN-38 (**5**) Figure 16.3). Several reviews of this phase of research have been published [10–12].

Together with the synthesis and screening of new derivatives and analogs, research continued unabated to unveil the details of the mechanism of action of CPT at the molecular level. The decade 1995–2005 brought new exciting results and some changes in the perspective of research in the CPT field [13].

Camptothecin acts by forming a reversible ternary complex (''cleavable complex'') with DNA and topoisomerase I, preventing the re-ligation of the DNA strand cut by topoisomerase to allow relaxation, and thus inducing apoptosis [14]. The X-ray structure of crystals of such a complex of a 22-base DNA fragment with topoisomerase I and topotecan has been reported [15], and molecular models of the interaction have been proposed [16–18]. This kind of information should be of help in

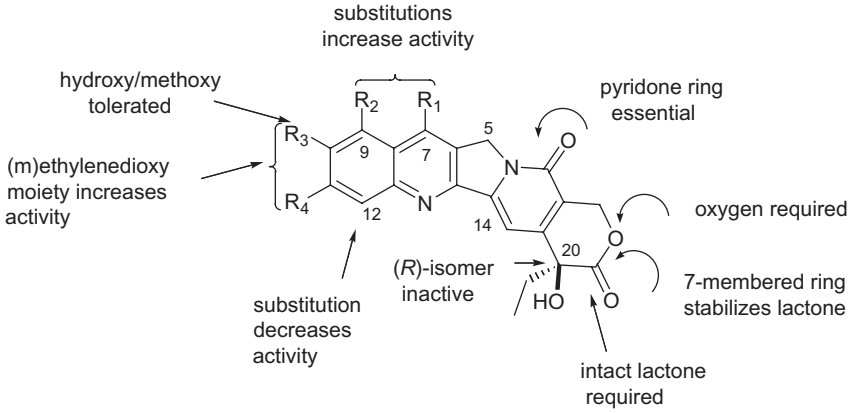


Fig. 16.2 Structure–activity relationships for antitumor activity in camptothecins as known around 1995.

designing new active compounds, but so far no breakthrough substance seems to have been obtained on such a basis, and discussion on which feature of ring E of camptothecin is essential for activity is still lively [19].

Over the years, the feature of interest for pharmacologists in camptothecins has progressively shifted, so that water solubility is no longer an essential requisite. Lipophilic compounds have the advantage of compartmentation in tissues, thus assuring the stabilization and enhanced persistence of the active lactone form, and allowing oral administration of the drug, with increased compliance by the patients. A seminal paper in this respect was published by Burke in 1993 [20], and now this trend is largely accepted [21]. These changes had important consequences in the design and synthesis of new analogs. In fact a series of lipophilic analogs of CPT are in preclinical development at the time of writing (2006) (Figure 16.4).

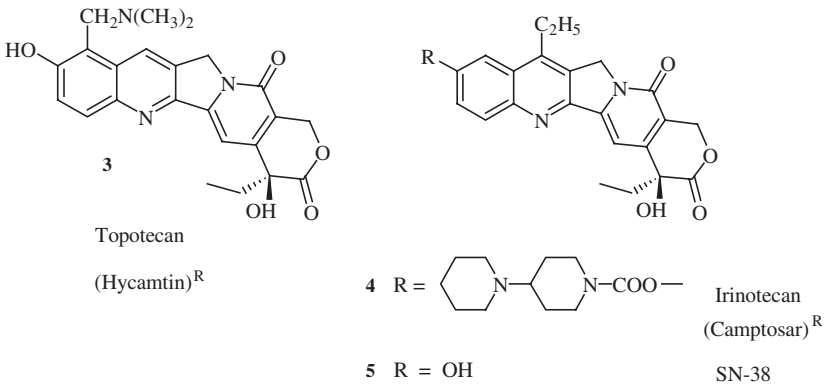


Fig. 16.3 Structures of topotecan and irinotecan.

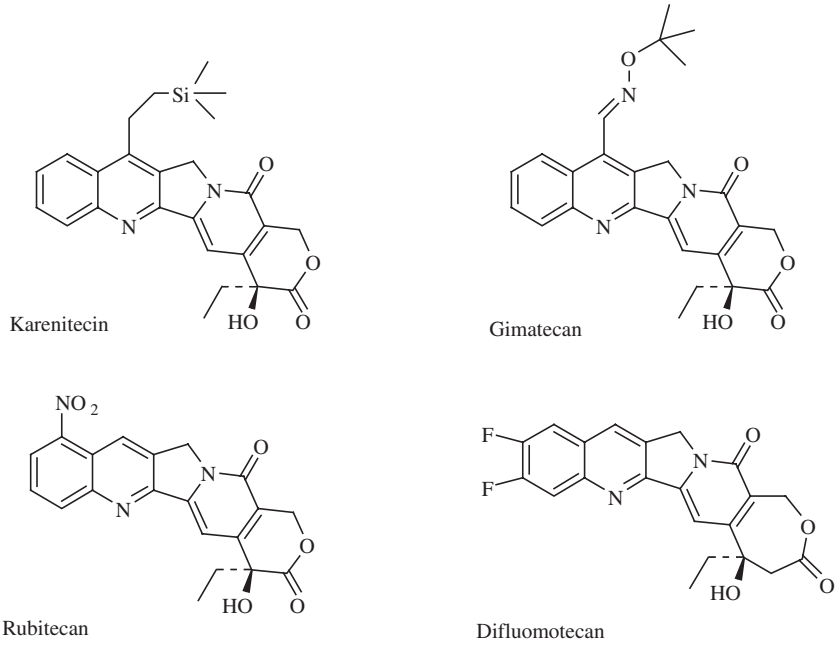


Fig. 16.4 Lipophilic analogs of camptothecin in clinical development.

Another aspect of the progress toward the development of a camptothecin drug candidate concerns the study of proper formulations, such as liposomes [22], and the finding of innovative drug delivery systems [23].

16.2 Synthetic Efforts

For the synthesis of a new camptothecin derivative, the first choice is between a semisynthesis starting from the natural compound CPT, or a total synthesis. Camptothecin is a chiral compound, with only one asymmetric center, carbon 20, the active compounds possessing the natural configuration (*S*). A semisynthesis has the advantages of starting from a compound that possesses all the necessary structural features, including the required 20-(*S*) configuration. The drawbacks of this approach can be the limited reactivity of the quinoline nucleus and the sensitivity of the lactone ring. For the development of a drug, difficulties could derive from the possible failure of an adequate and constant supply of the natural material, and from an unpredictable pattern of impurities in the different batches. Owing to the high potency of the drugs, doses are rather low, so that the amount of camptothecin required has so far been within the capacity of the Chinese and Indian producers, although some concern has been raised on the conservation of *Camptotheca acuminata*, which grows only in an area of China south of the Yangtze river. However,

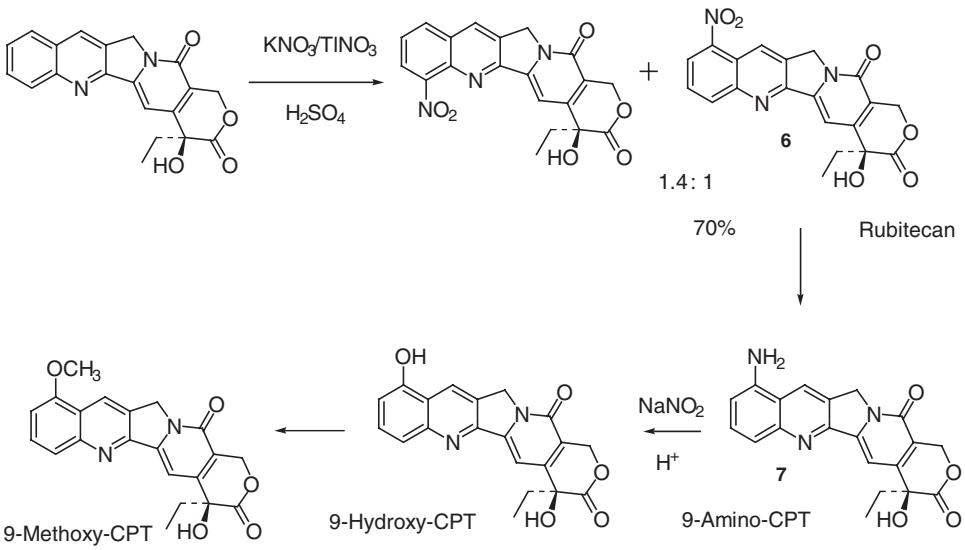
the plant has been shown to grow in other areas of the world, and considerable effort has already been spent toward the production of camptothecin by cell cultures [3].

On the other hand, a total synthesis offers the possibility of substitutions and structural modifications that depend only on the manageability of the synthetic scheme, so enlarging the diversity of the target compounds, and is free from the constraints indicated above. However, an asymmetric synthesis is required, with several steps, and so far most of the total syntheses appear too expensive. Actually, the two drugs currently in clinical practice and most of the candidates presently (2006) in an advanced stage of development are produced by semisynthesis.

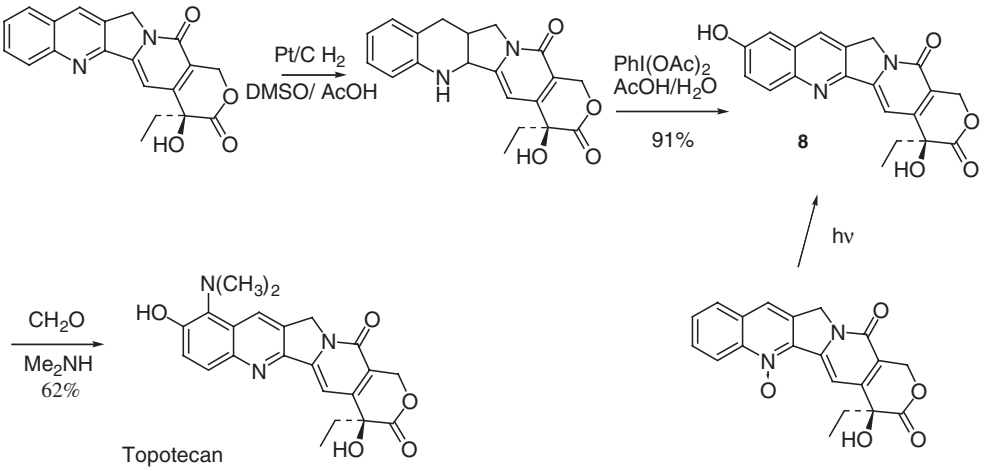
As Figure 16.2, 16.3 and 16.4 show, so far the most fruitful modifications of CPT to obtain an active antitumor compound have been the introduction of substituents in positions 7,9, and 10.

The electron-deficient ring of quinoline is not very reactive to electrophilic substitution, the preferred sites of attack being position 5 and 9 [24]. Nitration of CPT (best yields 70 % [25]) gives in fact a mixture of 12- and 9-nitrocamptothecin (**6**). The latter is itself a compound (Rubitecan) endowed with potent antitumor activity [26], and is a precursor of many derivatives, as it can be easily reduced to 9-amino-CPT (**7**), in turn convertible into 9-hydroxy- and 9-methoxycamptothecin, minor components of the plant extract (Scheme 16.3).

The accessibility of position 9 becomes much higher when an activating group, such as an OH, is present in position 10. Although 10-hydroxycamptothecin (**8**) is available in small amounts from the plant material, two efficient preparations of this compound were developed, via catalytic reduction of CPT in acid medium to a tetrahydroquinoline, followed by selective oxidation with lead tetraacetate [8], or phenyliodonium diacetate [27], or via a photochemical rearrangement of camptothe-



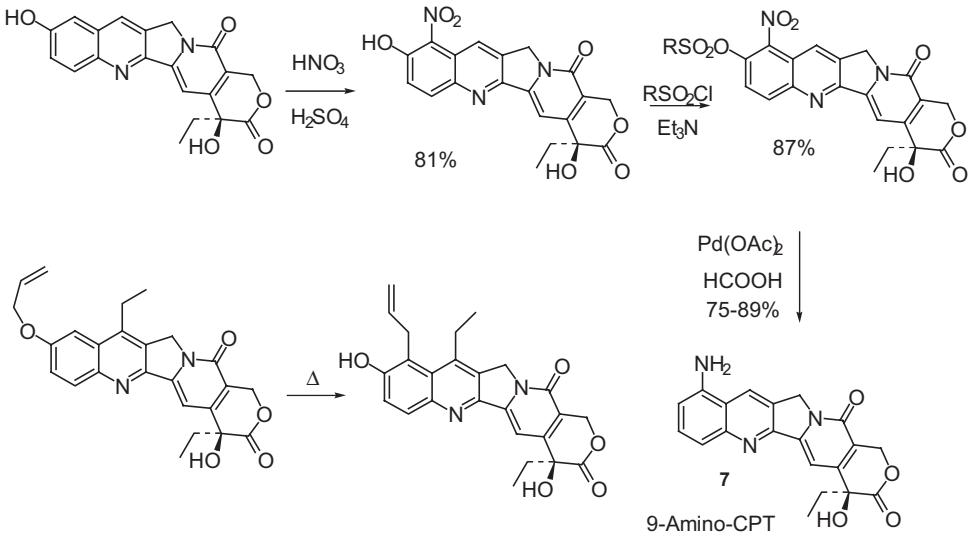
Scheme 16.3 Nitration of CPT and synthesis of 9-substituted CPTs.



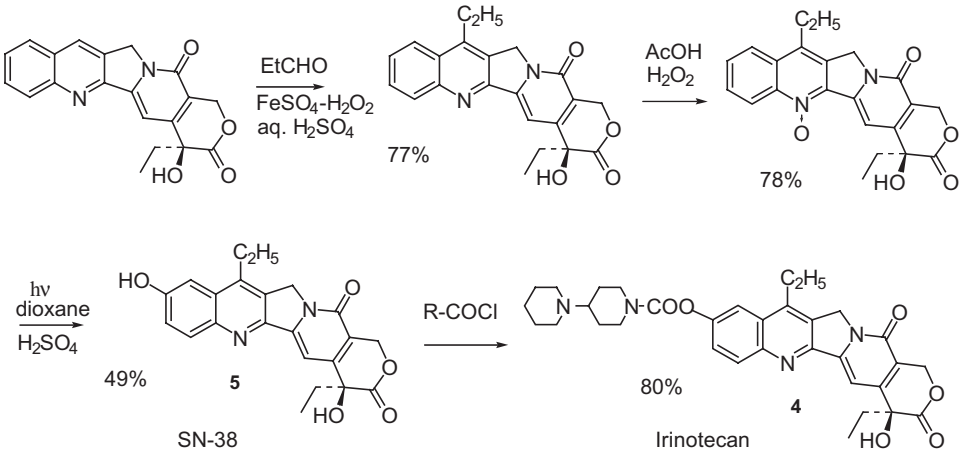
Scheme 16.4 Semisynthesis of topotecan.

cin *N*-oxide [28]. Thus activated, the nucleus smoothly undergoes the Mannich reaction to give topotecan (**3**) (Scheme 16.4).

The 10-hydroxy group can facilitate the alkylation of C-9 via a Claisen rearrangement, as in the case of 7-ethyl-10-hydroxy-CPT [29], or nitration in the same position, possibly followed by removal of the OH and reduction of the nitro group by palladium-catalyzed deoxygenation to give 9-aminoCPT (**7**)[30], another drug candidate (Scheme 16.5).



Scheme 16.5 Transformations of 10-hydroxycamptothecin.

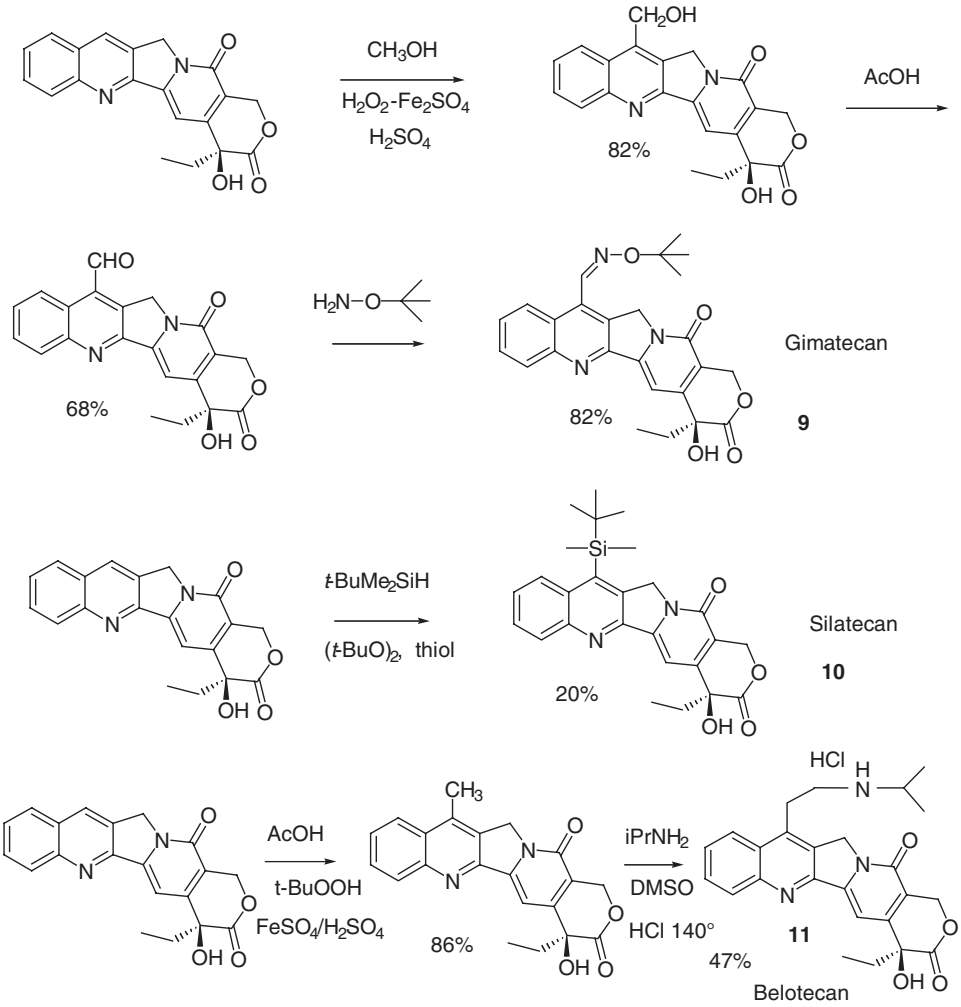


Scheme 16.6 Semisynthesis of irinotecan.

By contrast, substitution in position 7 is much easier thanks to the well-known Minisci reaction, which involves a nucleophilic radical attack on a protonated quinoline [31]. Moreover, due to the unavailability of position 2 of the quinoline nucleus, the reaction shows complete regioselectivity. Minisci alkylation with an ethyl radical produced *in situ* by decarbonylation of propionaldehyde is a crucial step in the process of preparation of irinotecan (**4**) (Scheme 16.6) [32], whereas the same kind of reaction led to the semisynthesis (Scheme 16.7) of gimatecan (**9**)[33], silatecan (**10**)[34], and belotecan (**11**)[35]. This last compound entered clinical practice in Korea in 2005.

A semisynthetic approach was also followed in the first synthesis of a camptothecin with a 7-membered lactone ring (**12**). This was indeed the first and so far the only modification of the E ring to give a strongly active compound. Lavergne and Bigg [36,37] reasoned that the reactivity of the lactone ring could be reduced by shifting the OH group from the α to the β position with respect to the lactone carbonyl. The modification was accomplished by reduction of CPT to a lactol, dehydration, and periodate oxidation followed by a Reformatzky reaction (Scheme 16.8).

As soon as the structure of camptothecin was published, the interest of many chemists, including some famous names, was directed toward this synthetic goal, encouraged by the relevance of the unusual antitumor activity. Later, when the compound had lost its novelty value, such studies were stimulated by the desire to achieve a process of production of the drugs derived from CPT and the preparation of new derivatives. Although at first sight the synthesis of CPT might not appear, by modern standards, a difficult task, the array of functional groups on ring E, not easily compatible with many synthetic procedures, has often required a number of steps and some detours to overcome the difficulties of a total synthesis. In some cases, the problem has been solved by the invention of new synthetic methods, so that the approaches have led to the addition of new tools to the arsenal of the synthetic organic chemist.

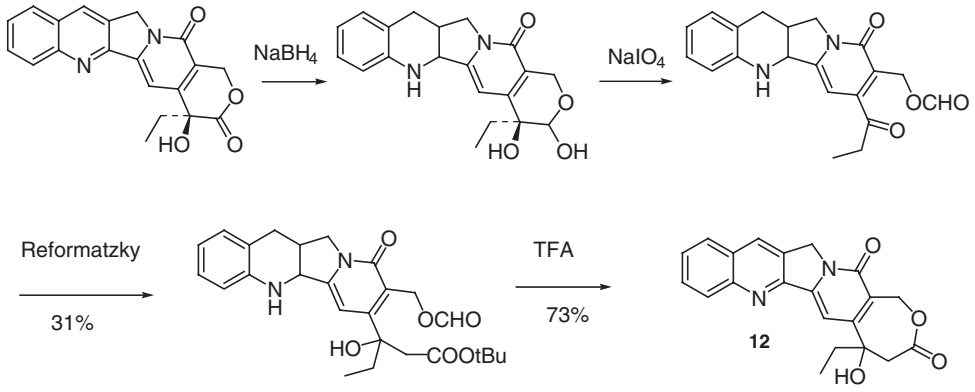


Scheme 16.7 Minisci reactions in the semisynthesis of camptothecin-derived drug candidates.

The early syntheses have been reviewed by Schultz [38] and Hutchinson [39]. Other reviews, more medicinally oriented, have appeared [40]. One of the most recent and detailed, covering work from 1990 onward, is that of Du [41].

As it is not possible to review here the large number of different syntheses of CPT, we will only attempt to call the attention of the reader to some particular or relevant, in our biased view, aspects of the large portfolio of synthetic approaches to camptothecins.

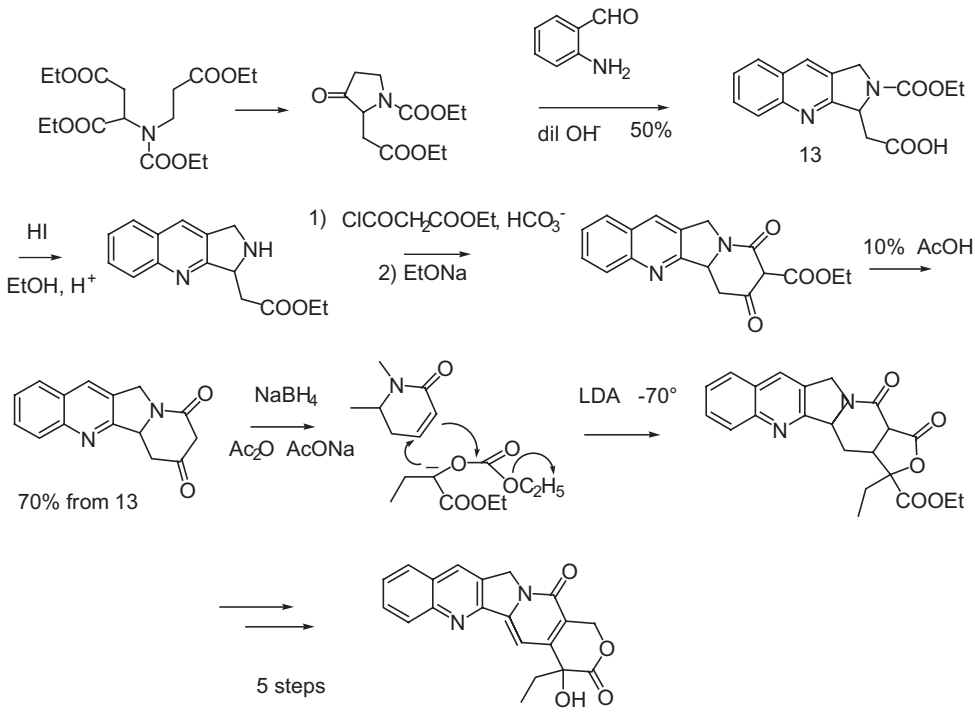
Some of the best organic chemists of the time, such as Stork, Danishefsky, and Corey, developed the early syntheses. The Stork synthesis of the racemate [42] was the first to use one of the most fruitful and popular approaches to the CPT skeleton, that is the building of ring B with a Friedländer synthesis (Scheme 16.9), but which



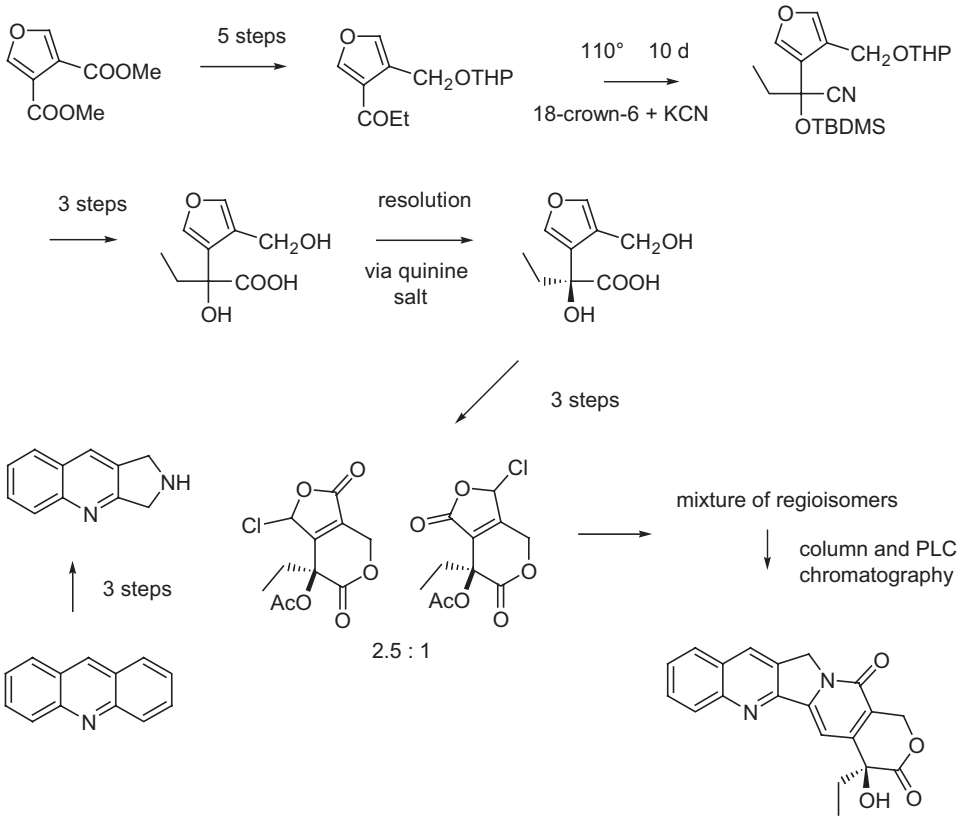
Scheme 16.8 Semisynthesis of racemic homocamptothecin.

encountered the problem of the conversion of a five-membered to a six-membered ring E, a difficulty experienced later by others.

The Corey synthesis [43] is worth revisiting for the originality of the approach in the construction both of ring C and of the D–E ring moiety, although it is flawed by the



Scheme 16.9 Stork synthesis of racemic CPT.

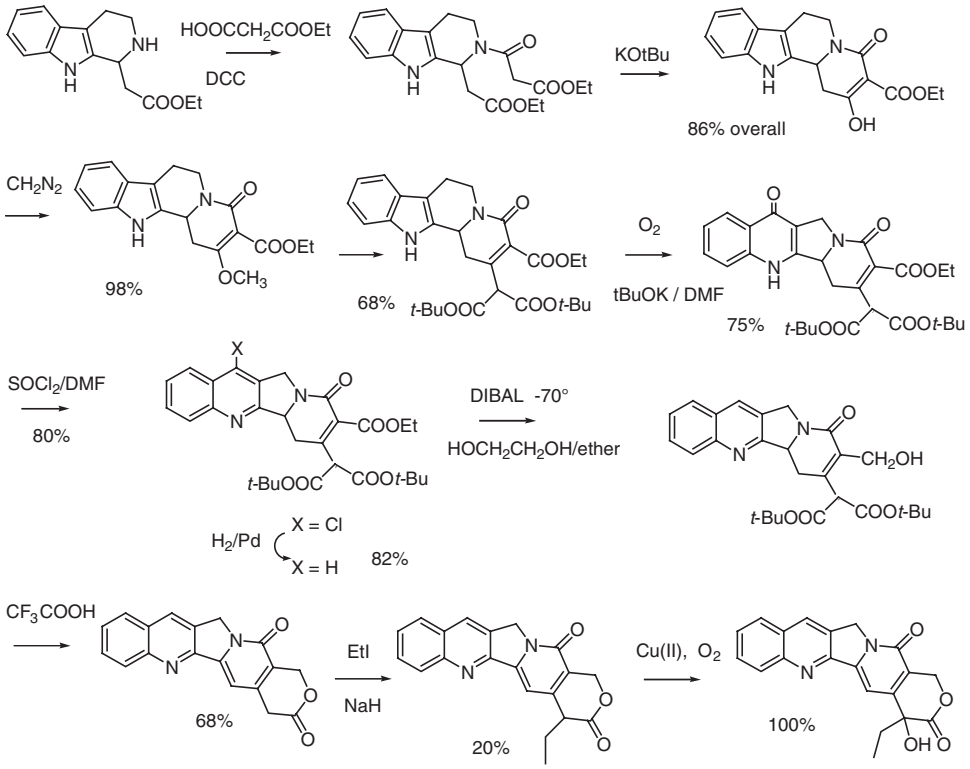


Scheme 16.10 Corey synthesis of 20(*S*)-camptothecin.

length of the preparation of the latter, and by lack of regioselectivity in the joining step (Scheme 16.10).

The Winterfeldt synthesis [44] of racemic camptothecin is remarkable for being the first to follow a biomimetic pathway, that is of taking advantage of the wealth of synthetic methods for indole alkaloids to synthesize the intermediate pyrido[3,4-b]indole intermediate to be converted by a biosynthetic-like oxidation into the expected pyrrolo[3,4-b]quinoline ring system. Moreover, this synthesis used simple and cheap reagents throughout (Scheme 16.11). Here, the last step could easily be made enantioselective by the use of a chiral hydroxylating reagent, such as Davis oxaziridines. Another truly biomimetic synthesis, but mostly only of academic interest, starting from strictosidine lactam, was reported by Brown [45].

As early as 1986, both Wall and coworkers [46] and a Chinese group [47] recognized the potentiality of a Friedländer synthesis approach from 2-aminobenzaldehyde with the synthon **14** and developed an approach to racemic **14**, based on the extremely efficient condensation of ethyl acetoacetate with cyanacetamide by Henecka [48], which provides in one step a pyridone intermediate **15** with three different sub-

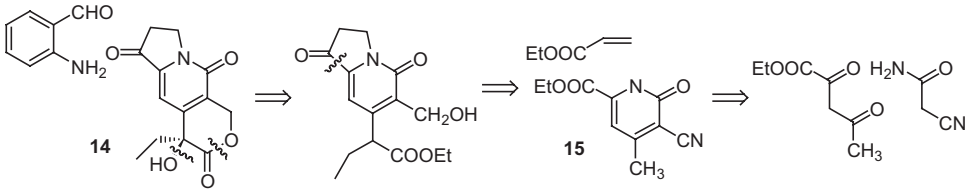


Scheme 16.11 Winterfeldt synthesis.

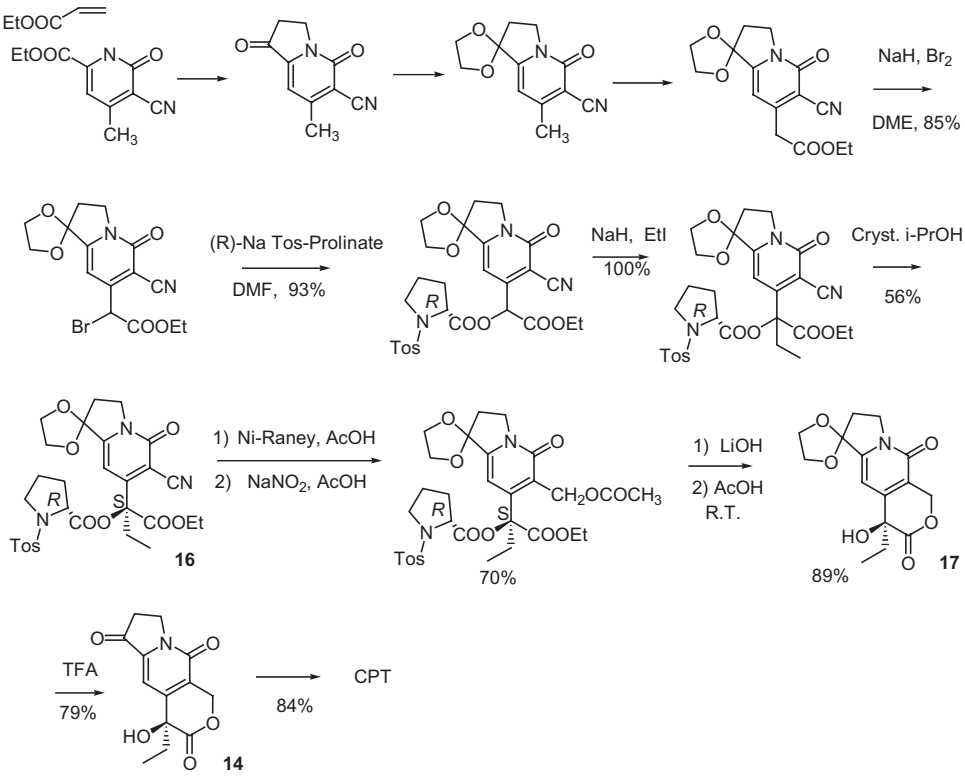
stituent in the strategic positions. Elaboration of **15** and condensation with ethyl acrylate afforded **14** (Scheme 16.12).

Subsequent effort by various groups was dedicated to improvement of the scheme to provide an efficient synthesis of chiral **14**, via chemical [49] or enzymatic resolution [50] or, as in Tagawa's synthesis (Scheme 16.13), the use of a chiral auxiliary [51]. A procedure to recycle the otherwise wasted (*R,R*)-diastereoisomer of **16** via conversion to the mesylate of *ent*-**17** and inversion with CsOAc was also reported [52], as well as a variant to obtain the desired enantiomer via Sharpless dihydroxylation [53].

Among the more recent achievements, the Comins approach capitalized on progress in the formation of sp^2–sp^2 C—C bonds with palladium chemistry to



Scheme 16.12 Approach to CPT synthesis via Friedländer condensation.



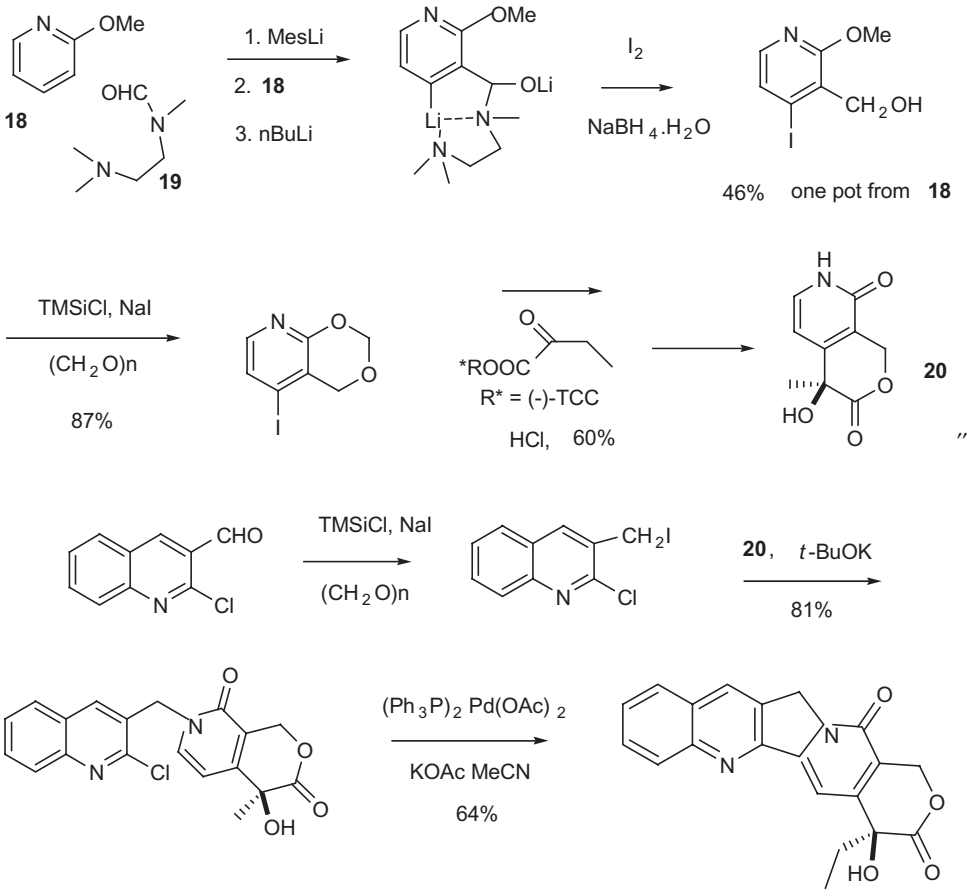
Scheme 16.13 Tagawa asymmetric synthesis of intermediate 14.

build ring C and on developments in the functionalization of pyridine by metallation [54]. For sake of brevity, Scheme 16.14 reports the final achievement, that is a six-step synthesis of CPT [55], but the reader is heartily invited to follow the masterly refinement and simplification of the synthesis across the series of Comins' papers [55–59]. It is a very instructive and enjoyable path.

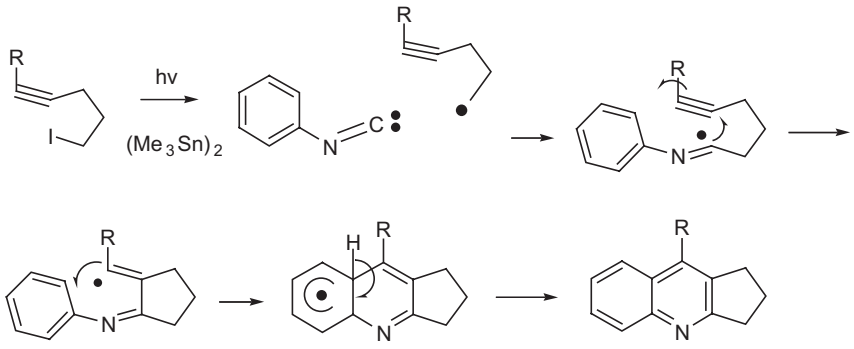
On the basis of preceding experience in the synthesis of methylenecyclopentanes, Curran discovered a cascade reaction proceeding via a 4 + 1 radical annulation mechanism that led to a new synthesis of cyclopenta-fused quinolines [60] (Scheme 16.15).

The extension of this route to the case of (±)-camptothecin [61] was followed by a series of improvements [62,63], where the key intermediate **21** was obtained via the Sharpless dihydroxylation previously proposed by Fang [64] or via an asymmetric cyanosilylation reaction [65] (Scheme 16.16).

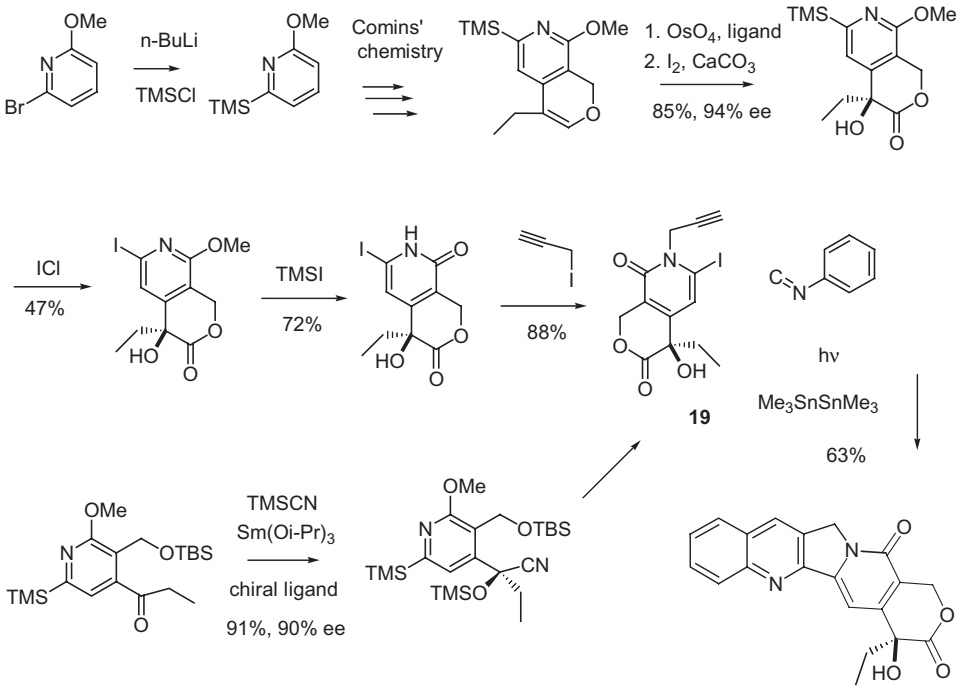
From a medicinal chemistry point of view, this approach can provide a wealth of camptothecins diversely substituted both in ring A, owing to the availability of anilines, immediate precursors of isonitriles, and at position 7, working on thepropargyl intermediates. Whereas para- and ortho-substituted isonitriles gave a regioselective cyclization, 3-substituted isonitriles gave a mixture of 9- and



Scheme 16.14 Comins shortest synthesis of CPT.



Scheme 16.15 Curran radical annulation to cyclopenta [2,3-b]quinolines.

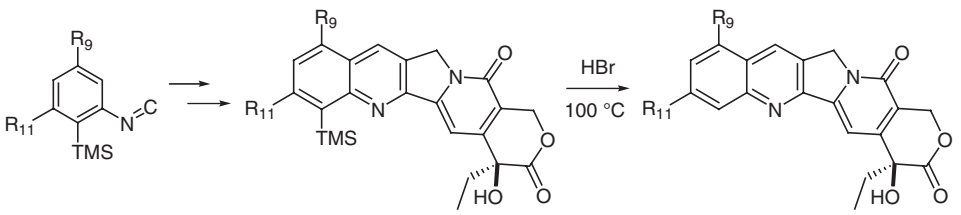


Scheme 16.16 Curran synthesis of (+)-camptothecin.

11-substituted camptothecins. This problem was circumvented by using the easily removable trimethylsilyl group as a temporary protection [66] (Scheme 16.17).

The radical cascade synthesis was applied to the preparation of drugs such as irinotecan [62], and drug candidates such as lurtotecan [66], silatecan DB-67 [67] and homosilatecans [68]. Moreover, a convergent synthesis could be applied to a combinatorial synthesis, in which over one hundred homosilatecans were prepared by parallel synthesis and automated purification [69].

The years since 1985 have seen an enormous amount of work aimed at unravelling many facets of the reactivity of camptothecin and developing fast and ingenious syntheses. Although many of the synthetic issues concerning camptothecin have



Scheme 16.17 Regioselective Curran synthesis of 9- and 11-substituted camptothecins.

been addressed, there is still room for the discovery of new straightforward and efficient methods of building the core ring system and of obtaining more specifically targeted derivatives and analogs. Future years will certainly bring exciting results toward these goals.

References

1 Wall, M. E., Wani, M. C., Cooke, C. E., Palmer, K. T., McPhail, A. T., Sim, G. A. (1966) *Journal of the American Chemical Society*, **88**, 3888–3890.

2 Govindachari, T. R. and Viswanathan, N. (1972) *Indian Journal of Chemistry*, **10**, 53–454.

3 Lorence, A. and Nessler, C. L. (2004) *Phytochemistry*, **65**, 2735–2749.

4 Hutchinson, C. R., Heckerdorf, A. H., Straughn, J. L., Daddona, P. E., Cane, D. E. (1979) *Journal of the American Chemical Society*, **101**, 3358–3366.

5 Yamazaki, Y., Kitajima, M., Arita, M., Takayama, H., Sudo, H., Yamazaki, M., Aimi, N., Saito, K. (2004) *Plant Physiology*, **134**, 161–170.

6 Moertel, C. G., Schutt, A. J., Reitemeyer, R. J., Hahn, R. G. (1972) *Cancer Chemotherapy Reports*, **56**, 95–101.

7 Hsiang, Y. -H., Hertzberg, R., Hecht, S., Liu, L. F. (1985) *Journal of Biological Chemistry*, **260**, 14873–14878.

8 Kingsbury, W. D., Boehm, J. C., Jakas, D. R., Holden, K. G., Hecht, S. M., Gallagher, G., Caranfa, M. J., McCabe, F. L., Faucette, L. F., Johnson, R. K., Hertzberg, R. P. (1991) *Journal of Medicinal Chemistry*, **34**, 98–107.

9 Kunimoto, T., Nitta, K., Tanaka, T., Uehara, N., Baba, H., Takeuchi, M., Yokokura, T., Sawada, S., Miyasaka, T., Mutai, M. (1987) *Cancer Research*, **47**, 5944–5947.

10 Potmesil, M.and Pinedo, H. (1995) *Camptothecins: New Anticancer Agents*, CRC Press, USA.

11 Pantaziz, P. and Giovanella, B. C. (1996) *The Camptothecins: From Discovery to Patient*, Annals of the New York Academy of Sciences, Vol. **803**.

12 Liehr, J. G., Giovanella, B. C., Verschraegen, C. F. Eds. (2000) *The Camptothecins: Unfolding Their Anticancer Potential*, Annals of the New York Academy of Sciences, Vol. 922 .

13 Thomas, C. J., Rahier, N. J., Hecht, S. M. (2004) *Bioorganic and Medicinal Chemistry*, **12**, 1585–1604.

14 Liu, L. F., Desai, S. D., Li, T. -K., Mao, Y., Sun, M., Sim, S. -P., Liehr, J. G., Giovanella, B. C., Verschraegen, C. F. (eds) (2000) Annals of the New York Academy of Sciences, 922, 1.

15 Staker, B. L., Hjerrild, K., Feese, M. D., Behnke, C. A., Burgin, A. B., Jr., Stewart, L. (2002) *Proceedings of the National Academy of Sciences*, **99**, 15387–15392.

16 Redinbo, M. R., Stewart, L., Kuhn, P., Champoux, J. J., Hol, W. G. (1998) *Science*, **279**, 1504–1513.

17 Fan, Y., Weinstein, J., Kohn, K. W., Shi, L. M., Pommier, Y. (1998) *Journal of Medicinal Chemistry*, **41**, 2216–2226.

18 Kerrigan, J. E. and Pilch, D. S. (2001) *Biochemistry*, **40**, 9792–9798.

19 Hecht, S. M. (2005) *Current Medicinal Chemistry: Anti-Cancer Agents*, **5**, 353–362.

20 Burke, T. G., Mishra, A. K., Wani, M. C., Wall, M. C. (1993) *Biochemistry*, **32**, 5352–5364.

21 Zunino, F., Dallavalle, S., Laccabue, D., Beretta, G., Merlini, L., Pratesi, G. (2002) *Current Pharmaceutical Design*, **8**, 99–110.

22 Hofheinz, R. -D., Gnad-Vogt, S. U., Beyer, U., Hochhaus, A. (2005) *Anti-Cancer Drugs*, **16**, 691–707.

23 Haag, R. and Kratz, F. (2006) *Angewandte Chemie, International Edition*, **45**, 1198–1215.

24 Schofield, K., Crout, D. H. G., Penton, J. R. (1971) *Journal of the Chemical Society B*, 1254–1256.

25 Cao, Z., Armstrong, K., Shaw, M., Petry, E., Harris, N. (1998) *Synthesis*, 1724–1730.

26 Clark, J. W. (2006) *Expert Opinion on Investigational Drugs*, **15**, 71–79Z.

27 Wood, J. L., Fortunak, J. M., Mastrocola, A. R., Mellinger, M., Burk, P. L. (1995) *Journal of Organic Chemistry*, **60**, 5739–5740.

28 Sawada, S., Matsuoka, S., Nokata, K., Nagata, H., Furuta, T., Yokokura, T., Miyasaka, T. (1991) *Chemical and Pharmaceutical Bulletin*, **39**, 3183–3188.

29 Gao, H., Zhang, X., Chen, Y., Shen, H., Sun, J., Huang, M., Ding, J., Li, C., Lu, W. (2005) *Bioorganic and Medicinal Chemistry Letters*, **15**, 2003–2006.

30 Cabri, W., Candiani, I., Zarini, F., Penco, S., Bedeschi, A. (1995) *Tetrahedron Letters*, 9197–9200.

31 Reviews on the subject: Minisci, F. (1973) *Synthesis*, 1–24. Topics in Current Chemistry (1976) 62, 1–48. Minisci, F., Vismara, E., Fontana, F. (1989) *Heterocycles*, **28**, 489–519. Minisci, F., Fontana, F., Vismara, E., *Journal of Heterocyclic Chemistry*, **27**, (1990) 79–96.

32 Sawada, S., Okajima, S., Aiyama, R., Nokata, K., Furuta, T., Yokokura, T., Sugino, E., Yamaguchi, K., Miyasaka, T. (1991) *Chemical and Pharmaceutical Bulletin*, **39**, 1446–1450.

33 Dallavalle, S., Ferrari, A., Biasotti, B., Merlini, L., Penco, S., Gallo, G., Marzi, M., Tinti, M. O., Martinelli, R., Pisano, C., Carminati, P., Carenini, N., Beretta, G., Perego, P., De Cesare, M., Pratesi, G., Zunino, F. (2001) *Journal of Medicinal Chemistry*, **44**, 3264–3274.

34 Du, W., Kaskar, B., Blumbergs, P., Subramanian, P. K., Curran, D. P. (2003) *Bioorganic and Medicinal Chemistry*, **11**, 451–458.

35 Ahn, S. K., Choi, N. S., Jeong, B. S., Kim, K. K., Journ, D. J., Kim, J. K., Lee, S. J., Kim, J. W., Hong, C., Jew, S. -S. (2000) *Journal of Heterocyclic Chemistry*, **37**, 1141.

36 Lavergne, O., Lesueur-Ginot, L., Rodas, F. P., Bigg, D. C. H. (1997) *Bioorganic and Medicinal Chemistry Letters*, **7**, 2235–2238.

37 Lavergne, O., Lesueur-Ginot, L., Rodas, F. P., Kasprzyk, P. G., Pommier, J., Demarquay, D., Prevost, G., Ulibarri, G., Rolland, A., Schiano-Liberatore, A., Harnett, J., Pons, D., Camara, J., Bigg, D. C. H. (1998) *Journal of Medicinal Chemistry*, **41**, 5410–5419.

38 Schultz, A. G. (1973) *Chemical Reviews*, **73**, 385–405.

39 Hutchinson, C. R. (1981) *Tetrahedron*, **37**, 1047–1065.

40 (a) Wall, M.E. and Wani, M. C. (1994) Camptothecin. In Saxton, J.E. *The Monoterpenoid Indole Alkaloids*, Wiley, London. (b) Kawato, Y. and Terasawa, H. (1997) *Progress in Medicinal Chemistry*, **34**, 69–109 (c) Baurle, S. and Koert, U. (2000) Camptothecin –Synthesis of an Antitumor Agent. In *Organic Synthesis Highlights* IV (ed. H. G. Schmalz), pp. 232–240.

41 Du, W. (2003) *Tetrahedron*, **59**, 8649–8687.

42 Stork, G. and Schultz, A. G. (1971) *Journal of the American Chemical Society*, **93**, 4074–4075.

43 Corey, E. J., Crouse, D. N., Anderson, J. E. (1975) *Journal of Organic Chemistry*, **40**, 2140–2141.

44 Boch, M., Korth, T., Nelke, J. M., Pike, D., Radunz, H., Winterfeldt, E. (1972) *Chemische Berichte*, **105**, 2126–2142. Krohn, K. and Winterfeldt, E. (1975) *Chemische Berichte*, **108**, 3030. Krohn, K., Ohlendorf, H. -W., Winterfeldt, E. (1976) *Chemische Berichte*, **109**, 1389–1394.

45 Brown, R. T., Liu, J., Santos, C. A. M. (2000) *Tetrahedron Letters*, **41**, 859–862.

46 Wall, M. E., Wani, M. C., Natschke, S. M., Nicholas, A. W. (1986) *Journal of Medicinal Chemistry*, **29**, 1553–1555.

47 Kexue Tongbao, 21, 40–42 (1976) (Chemical Abstracts, 84, 122100n (1976)). Scientia Sinica, 21, 87–98 (1978).

48 Henecka, H. (1949) *Chemische Berichte*, **82**, 41–46.

49 Wani, M. C., Nicholas, A. W., Wall, M. E. (1987) *Journal of Medicinal Chemistry*, **30**, 1774–1779.

50 Imura, A., Itoh, M., Miyadera, A. (1998) *Tetrahedron: Asymmetry*, **9**, 2285–2291.

51 Ejima, A., Terasawa, H., Sugimori, M., Tagawa, H. (1990) *Journal Of The Chemical Society-Perkin Transactions 1*, 27–31.

52 Terasawa, H., Sugimori, M., Ejima, A., Tagawa, H. (1989) *Chemical and Pharmaceutical Bulletin*, **37**, 3382–3385.

53 Jew, S. -S., Ok, K. -D., Kim, H. -J., Kim, M. G., Kim, J. M., Hah, J. M., Cho, Y. -S. (1995) *Tetrahedron: Asymmetry*, **6**, 1245–1248.

54 Rocca, P., Cochennec, C., Marsais, F., Thomas-dit-Dumont, L., Mallet, M., Godard, A., Queguiner, G. (1993) *Journal of Organic Chemistry*, **58**, 7832–7838.

55 Comins, D. L. and Nolan, J. M. (2001) *Organic Letters*, **3**, 4255–4257.

56 Comins, D. L., Baevsky, M. F., Hong, H. (1992) *Journal of the American Chemical Society*, **114**, 10971–10972.

57 Comins, D. L., Hong, H., Gao, J. (1994) *Tetrahedron Letters*, **30**, 5331–5334.

58 Comins, D. L. and Saha, J. K. (1995) *Tetrahedron Letters*, **36**, 7995–77998.

59 Comins, D. L., Hong, H., Saha, J. K., Gao, J. (1994) *Journal of Organic Chemistry*, **59**, 5120–5121.

60 Curran, D. P. and Liu, H. (1991) *Journal of the American Chemical Society*, **113**, 2127–2132.

61 Curran, D. P. and Liu, H. (1992) *Journal of the American Chemical Society*, **114**, 5863–5864.

62 Curran, D. P., Ko, S. -B., Josien, H. (1996) *Angewandte Chemie, International Edition*, **34**, 2683–2684.

63 Curran, D. P., Liu, H., Josien, H., Ko, S. -B. (1996) *Tetrahedron*, **52**, 11385–11404.

64 Fang, F. G., Xie, S., Lowery, M. W. (1994) *Journal of Organic Chemistry*, **59**, 6142–6143.

65 Yabu, K., Masumoto, S., Kanai, M., Du, W., Curran, D. P., Shibasaki, M. (2003) *Heterocycles*, **59**, 369–385. and preceding papers

66 Josien, H., Ko, S. -B., Bom, D., Curran, D. P. (1998) *Chemistry—A European Journal*, **4**, 67–83.

67 Bom, D., Curran, P. D., Chavan, A. J., Kruszewski, S., Zimmer, S. G., Fraley, K. A., Bingcang, A. L., Latus, L. J., Pommier, Y., Burke, T. G. (2000) *Journal of Medicinal Chemistry*, **43**, 3970–3980.

68 Bom, D., Curran, P. D., Chavan, A. J., Kruszewski, S., Zimmer, S. G., Fraley, K. A., Burke, T. G. (1999) *Journal of Medicinal Chemistry*, **42**, 3018–3022.

69 Gabarda, A. E. and Curran, D. P. (2003) *Journal of Combinatorial Chemistry*, **5**, 617–624.