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Novel Syntheses of Camptothecin Alkaloids, Part 2.[1] Concise Synthesis of (*S*)-Camptothecins

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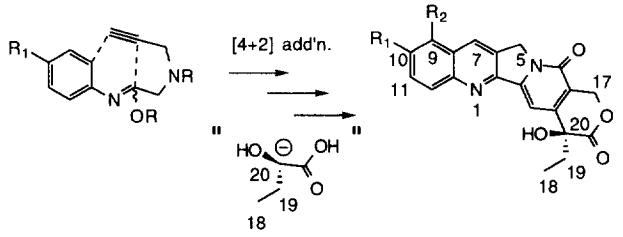
Abstract: A 9-step, convergent total synthesis of (*S*)-camptothecin alkaloids is described. The intramolecular [4+2] cycloaddition of an N-arylimidate with an alkyne is used to prepare the alkaloid ABC ring system.[1] The chiral center is derived utilizing Seebach's chemistry[2] for the diastereoselective Michael addition of a chiral dioxolanone enolate to a methylene malonate acceptor. The total synthesis of non-racemic topotecan is accomplished from (S)-10-hydroxycamptothecin in an additional step.

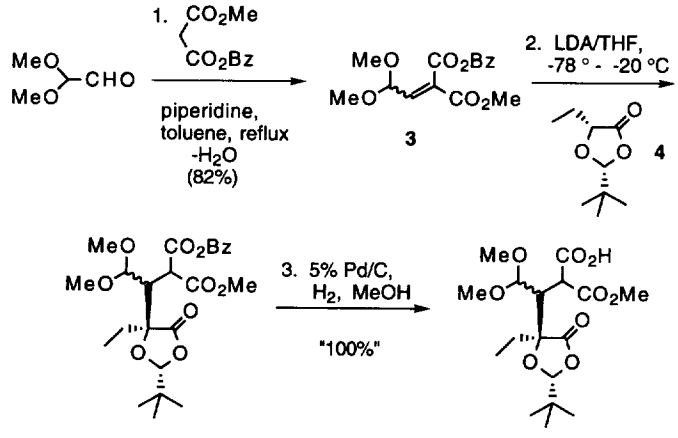


1 $R_1 = R_2 = H$ Camptothecin
2 $R_1 = OH$, $R_2 = CH_2NMe_2 \cdot HCl$ Topotecan(SmithKline Beecham)

In the preceding communication we described an intramolecular [4+2] cycloaddition approach to the camptothecin ABC (pyrrolo[3,4-b]quinoline) ring system.[1] We disclose here the use of a chiral, non-racemic 2-hydroxybutyric acid enolate equivalent to introduce C-(18-21) of camptothecin in the natural absolute configuration. In combination with our cycloaddition strategy this gave a synthesis of (*S*)-camptothecins in nine total steps from commercially available starting materials, with a longest linear sequence of six steps.[3]

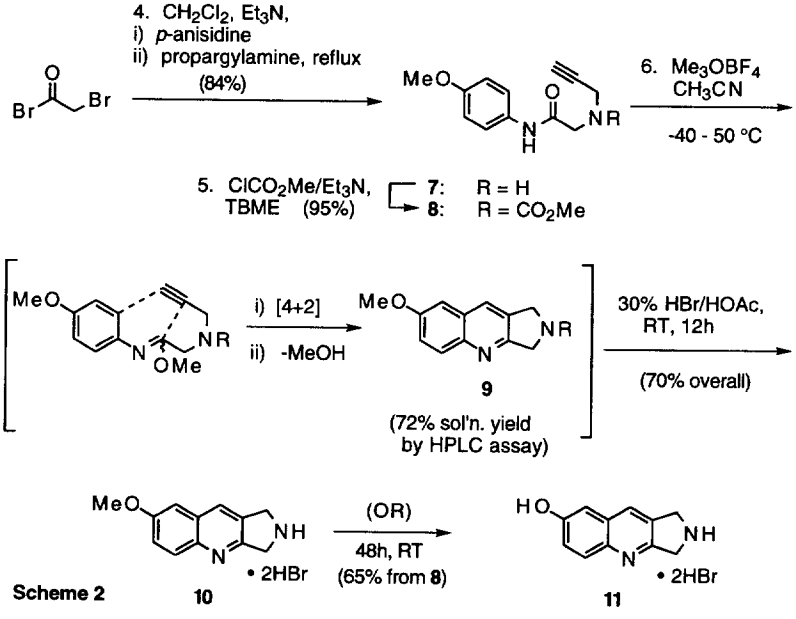
Separate, three step sequences were carried out to prepare intermediates **6** and **10** which were then coupled and carried on to complete our synthesis. Benzyl methyl malonate (Scheme 1) was condensed with glyoxal-1,1-dimethyl acetal[4,5] (piperidine/toluene, azeotropic removal of water) in 82% yield. The methylene(malonate) **3** was then utilized as a Michael acceptor to introduce of what will become C-(18-21) of the alkaloid. The enolate of (2*R*,5*R*)-2-*tert*-butyl-5-ethyl-1,3-dioxolan-4-one (**4**)[2,6-9] was prepared (LDA/THF, -78 °C) and added to **3** with warming to -20 °C before quenching with aqueous ammonium chloride. The crude product was isolated and reductively debenzylated to give the half-acid malonate **6** in essentially quantitative mass balance. Assignment of diastereoselectivity on the dioxolanone ring was complicated by the presence of multiple isomers in **5** and **6**. The degree of diastereoselection attained in setting the desired chiral center was therefore deferred until analysis could be carried out at the stage of intermediate **13** and, subsequently, for (*S*)-10-methoxycamptothecin.[8]

In a parallel sequence (Scheme 2) bromoacetyl bromide was first reacted with *para*-anisidine in methylene chloride:triethylamine, followed by an excess of propargylamine (1.8 eq., reflux) to give crystalline amine **7** in 84% yield. Protection of the amine as its methyl carbamate (95%) was followed by careful



Scheme 1

conversion of the N-aryl-amide to an intermediate O-methyl-imidate (2.5 eq. of freshly prepared trimethyloxonium tetrafluoroborate in acetonitrile at -40 °C). Intramolecular cycloaddition and elimination of methanol was carried out with slow heating to 50 °C to yield **9** in 72% solution yield as assayed by HPLC.[10]

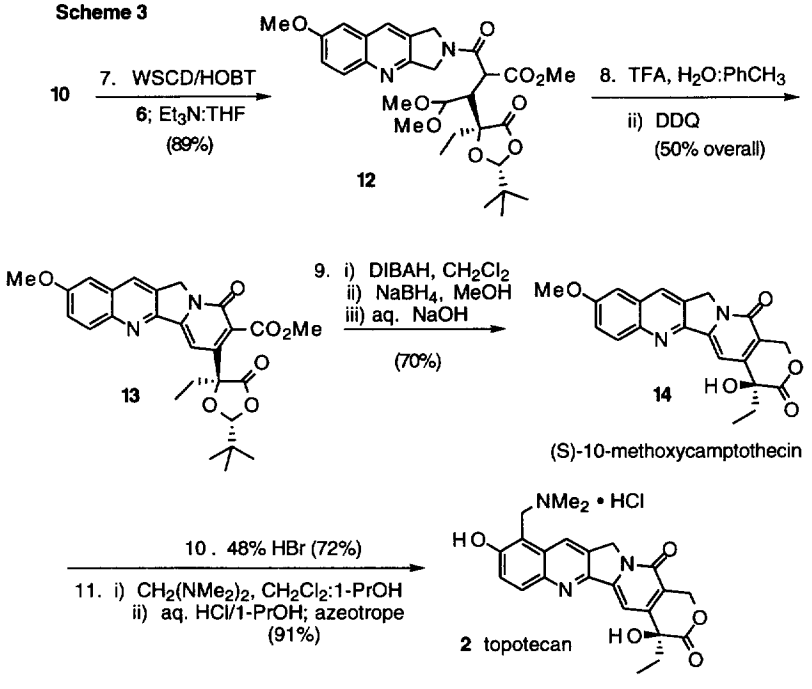


Scheme 2

Isolation of **9** was initially carried out to confirm its structure. It was more efficient, however, to directly add a solution of 30% hydrobromic acid in acetic acid at 20 °C (approximately 5 mol eq. of HBr) and remove the methyl carbamate without workup. The dihydrobromide salt of pyrrolo[3,4-b]quinoline **10** was then obtained in 70% overall yield from **8** by concentration and precipitation from the reaction solution.[11] Alternatively, removal of the methyl ether was also accomplished by stirring of the reaction suspension for a longer period of time (48 hours, 10 mol eq. of HBr) in 65% yield from **8**. Both **10** and **11** reacted with **6** to achieve syntheses of (*S*)-10-methoxy and (*S*)-10-hydroxycamptothecin, respectively. We describe here the

transformation of **10** to (*S*)-10-methoxycamptothecin and, subsequently, to topotecan. Coupling with acid **6** in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide/1-hydroxybenzotriazole[12] (WSCD, water-soluble carbodiimide) gave amide **12** in high yield. Hydrolysis of the dimethylacetal and subsequent aldolization to give the D-ring dihydropyridone was carried out similarly to Meyers *et al.*[3a,13,14] Addition of DDQ followed by workup then gave pyridone **13** from **12** in a single pot reaction. Reduction of the methyl ester with diisobutylaluminum hydride in methylene chloride followed by addition of sodium borohydride in methanol gave a mixture of the hydroxymethyl derivative and 10-methoxycamptothecin resulting from intramolecular opening of the dioxolanone ring and loss of pivalaldehyde. Complete conversion to **14** was therefore carried out without isolation by the addition of aqueous sodium hydroxide. Acidification of the reaction mixture with acetic acid gave (*S*)-10-methoxycamptothecin by direct precipitation. Recrystallization from methylene chloride:methanol gave the desired product in 70% yield from **13**.[15] The product was obtained in >99% chemical purity as determined by HPLC assay versus a reference standard. Chiral analysis by HPLC[16] showed that the product was obtained in an enantiomeric excess of 98.9%. This is in agreement with the determination that the cis-dioxolanone **4** was prepared in a diastereoselectivity of approximately 200:1 at carbon-5[9] and the expectation that alkylation of its enolate should be highly anti-selective.

Scheme 3



The methyl ether of **14** was removed with 48% hydrobromic acid to give 10-hydroxycamptothecin.[10] Mannich reaction with bis-(dimethylamino)-methane in methylene chloride:1-propanol followed by addition of aqueous hydrochloric acid and azeotroping with additional 1-propanol gave topotecan (91% yield) of >99.5% e.e. for the 20-(S) configuration. The overall yield for this synthesis of (S)-10-methoxycamptothecin is 17% based on bromoacetyl bromide (six linear steps). Topotecan was prepared in eleven total steps (longest linear sequence of eight steps) in 11% overall yield. All starting materials and reagents used are commercially available. We expect that this procedure could be further developed to meet commercial needs for camptothecin-based anticancer agents.

Modifications of this approach gave more convenient synthesis of topotecan in four total steps. We intend to publish a description of this chemistry in due course.

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References and Notes

1. Refer to the immediately preceding communication.
2. a) *cf.* Seebach, D. *Angew. Chem. Int'l. Ed. Engl.* **1990**, *29*, 1320 and quoted ref's.; b) Blaser, D.; Ko, S.Y.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 6230; c) Seebach, D.; *et al. Liebigs Ann.* **1989**, 1215; d) Blaser, D.; Seebach, D. *Liebigs Ann.* **1991**, 1067; e) Seebach, D.; Burger, H.M.; Schickli, C.P. *Liebigs Ann.* **1991**, 669; f) Suzuki, K.; Seebach, D. *Liebigs Ann.* **1992**, 51.
3. Previous asymmetric syntheses of camptothecin: a) Corey, E.J.; Crouse, D.N.; Anderson, J.E. *J. Org. Chem.* **1975**, *40*, 2140; b) Wani, M.C.; Nicholas, Q.W.; Wall, M.E. *J. Med. Chem.* **1987**, *30*, 2317; c) Ejima, A.; Terasawa, H.; Sugimori, M.; Tagawa, H. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 27; Ejima, A.; Terasawa, H.; Sugimori, M.; Tagawa, H. *Tetrahedron Lett.* **1989**, *30*, 2639; d) Comins, D.L.; Baevsky, M.F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971; Comins, D.L.; Salvador, J.M. *Tetrahedron Lett.* **1993**, *34*, 801; e) Curran, D.P.; Bo, S.-B.; Josien, H. *Angew. Chem. Int'l. Ed. Engl.* **1995**, *54*, 2683 and ref's. cited; f) Fang, F.G.; Xie, S., Lowery, M.W.; *J. Org. Chem.* **1994**, *59*, 6142.
4. Glyoxal-1,1-dimethyl acetal was obtained from the Aldrich Corp., alternatively this may be conveniently prepared according to references 5.
5. a) Stambouli, A.; *et al. Bull. Soc. Chim. Fr.* **1988**, 95; b) Chastrette, F.; *et al. Synth. Commun.* **1988**, *18*, 1343.
6. Purchased from Chiron Laboratories, A.S. The chiral dioxolanone may also be conveniently prepared from (*R*)-2-hydroxybutyric acid similarly to the description in reference 7.
7. Krohn, K.; Hamann, I. *Liebigs. Ann.* **1988**, 949.
8. It is well known that diastereoselectivity at carbon 5 of the dioxolanone ring is nearly always very high in alkylations of this sort; however, stereoselectivity at other carbon centers is usually poor, *cf.* refs. 4.
9. a) Chiral analysis of the (2*R*,5*R*)-cis-dioxolanone **4** by ^{1}H NMR using shift reagents showed approximately 200:1 for the (*R*)- vs. (*S*)-stereochemistry at carbon 5. Comparison with an authentic sample of the (2*S*,5*R*)-trans-dioxolanone as the minor product from the reaction (ref. 6) showed that levels were below the detectable limit by either NMR or GC analysis.
   b) (*R*)-2-hydroxybutyric acid was prepared from the corresponding amino acid, *cf.* Mori, K.; Sasaki, M.; Tamada, S.; Suguro, T.; Masuda, S. *Tetrahedron* **1979**, *35*, 1601.
10. A reference sample of **9** was prepared by isolation and repeated recrystallization. After determination of nominal absolute purity for this material the solution yields were determined by HPLC analysis on a weight/weight basis relative to standard solutions of the reference sample.
11. Wani, M.C.; Campbell, H.F.; Brine, G.A.; Kepler, J.A.; Wall, M.E.; Levine, S.G. *J. Am. Chem. Soc.* **1972**, *94*, 3631.
12. Kimura, T.; Takai, M.; Masui, Y.; Morikawa, T.; Sakakibara, S. *Biopolymers* **1981**, *20*, 1823.
13. Meyers, A.I. *et al. J. Org. Chem.* **1974**, *38*, 1973.
14. Rama Rao, A.V.; Yadav, J.S.; Valluri, M. *Tetrahedron Lett.* **1994**, *35*, 3613.
15. Authentic samples of (*S*)-10-methoxycamptothecin were obtained from *Camptotheca acuminata* (Sino-American Tianjin SK&F Labs Ltd., Tianjin, China). Also *cf.* Lin, L.-T.; Chao, T.-Y.; Hsu, J.-S. *Hva Hsueh Hsueh Pao*, **1977**, *35*, 277; *Chem. Abstr.* **1978**, *89*, 22078S.
16. Analysis conducted using two concatenated Techocel OA-3100 colums (total dimensions 4.0mm x 50cm) using 5% methanol in n-butylchloride as the mobile phase.

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