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A Practical Six-Step Synthesis of (*S*)-Camptothecin

Daniel L. Comins* and Jason M. Nolan

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204

daniel_comins@ncsu.edu

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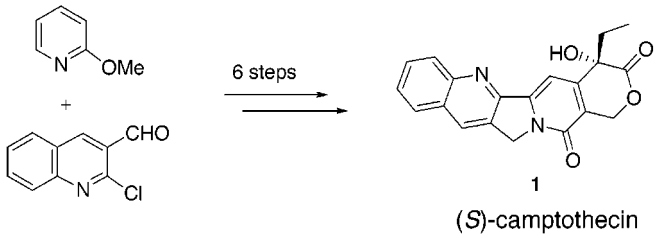
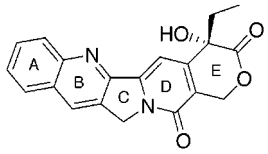
ABSTRACT



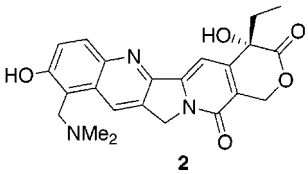
An asymmetric synthesis of (*S*)-camptothecin (1) has been accomplished in six steps starting from two commercially available heterocycles.

(*S*)-Camptothecin (CPT, **1**), a pentacyclic alkaloid isolated from *Camptotheca acuminata* by Wall and co-workers in 1966, is an important lead compound for the preparation of selective anticancer drugs.[1,2] The cytotoxic activity of CPT is attributed to a mechanism of action involving DNA and topoisomerase I, a process causing irreversible DNA damage and subsequent cell death.[3] Two CPT analogues, topotecan (**2**) and irinotecan (**3**), are now being used in clinical practice. Several other analogues are in various stages of clinical development.[4]

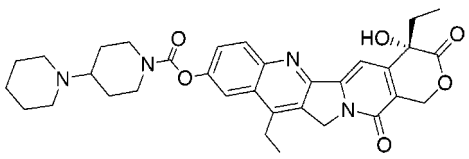
Since several syntheses of CPT and analogues have been developed over the years,[2] synthetic efforts now need to be directed at short, practical routes that are amenable to scale-up for drug preparation. For several years we have dedicated part of our research program to the development of short syntheses of CPT and derivatives. Through this effort we were able to achieve 10- and 9-step asymmetric syntheses



1
camptothecin



2
topotecan



3
irinotecan

(1) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888. (b) Wall, M. E.; Wani, M. C. *J. Ethnopharmacol*. **1996**, *51*, 239.

(2) Recent reviews: (a) Wall, M. E.; Wani, M. C. *Alkaloids* **1998**, *50*, 509. (b) "The Camptothecins: from Discovery to the Patient"; Pantaziz, P., Giovanella, B. C., Eds. *Ann. N. Y. Acad. Sci.* **1996**, 803. (c) *Camptothecins*: *New Anticancer Agents*; Potmesil, H.; Pinedo, H., Eds.; CRC Press: Boca Raton, FL, 1995.

(3) Holm, C.; Covey, J. M.; Kerrigan, D.; Pommier, Y. *Cancer Res.* **1989**, *49*, 6365.

(4) (a) Kim, D.-K.; Ryu, D. H.; Lee, J. Y.; Lee, N.; Kim, Y.-W.; Kim, J.-S.; Chang, K.; Im, G.-J.; Kim, T.-K.; Choi, W.-S. *J. Med. Chem.* **2001**, *44*. 1594. (b) 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. *J. Med. Chem.* **2001**, *44*, 3264 and references therein.

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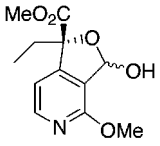
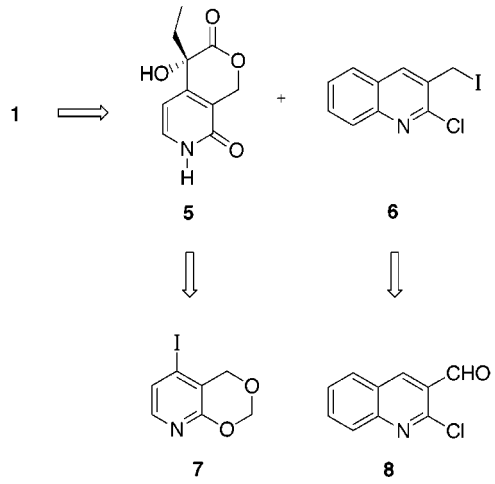
of (*S*)-CPT and a 6-step racemic synthesis.[5] We had hoped that our 6-step route could be modified to afford enantiopure (*S*)-CPT; however, our efforts at preparing the key intermediate **4** in an asymmetric fashion were unsuccessful. To



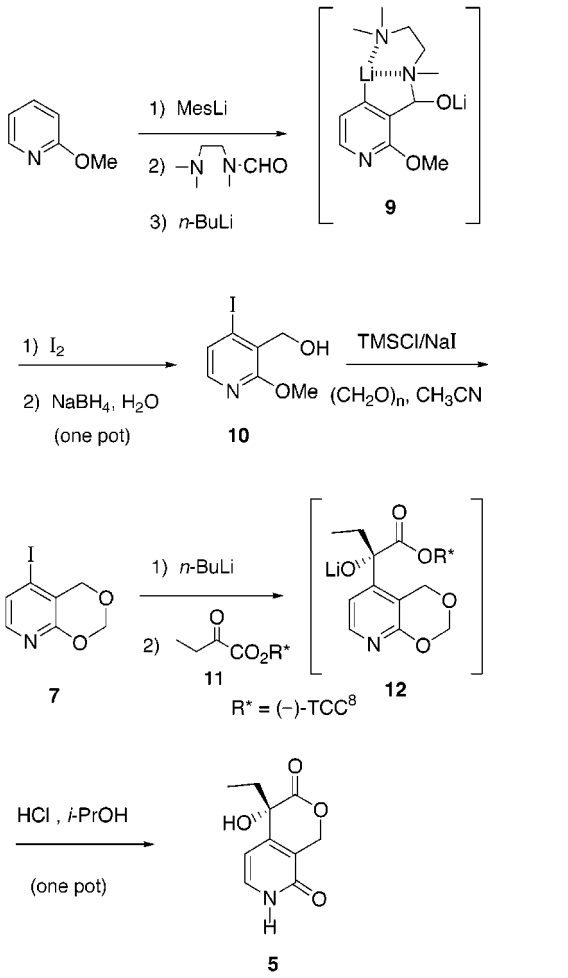
4

accomplish our goal of a 6-step asymmetric synthesis of CPT, we decided to explore the route depicted in Scheme 1.

Scheme 1



Scheme 2



To limit the total number of steps to six, the AB ring precursor **6** had to be prepared from quinoline derivative **8** in a single step. The DE ring fragment **5** would have to be made via intermediate **7** in only three steps from commercially available material. We now report the successful development of a 6-step CPT synthesis using this strategy.

To prepare the DE ring fragment **5** in three steps, a 2-step synthesis of intermediate **7** was required. Commercially available 2-methoxypyridine was lithiated at C-3 with mesityllithium[6] and treated with *N*-formyl-*N*,*N*′,*N*′-trimethylethylenediamine to give an α-amino alkoxide in situ (Scheme 2). Addition of *n*-BuLi effected α-amino alkoxide directed lithiation[7] at C-4 to give the dianion **9**. Addition of iodine and workup with aqueous $NaBH_4/CeCl_3$ provided a 46% yield of alcohol **10** via a one-pot process. After considerable effort, it was found that **10** could be converted directly to 1,3-dioxane **7** on treatment with NaI/TMSCl/paraformaldehyde in 87% yield. Conversion of **7** to CPT intermediate **5** was carried out in a single step. Lithium−halogen exchange was effected with *n*-BuLi followed by the addition of ketoester **11**[5b] to give alkoxide **12** in situ. Addition of HCl/*i*-PrOH effected protonation, acetal hydrolysis, and lactonization to afford the desired intermediate **5**. The crude material was extracted with hot hexanes to remove and recover (94%) the chiral auxiliary, (−)-TCC.[8] The remaining solid residue was purified by chromatography and recrystallization from methanol to afford a 60% yield of DE ring intermediate **5** as white crystals: mp 222−225 °C dec; $[\alpha]_D^{23}$ +117.0 (*c* 0.3, MeOH) (93% ee).

With the desired DE ring synthesis in hand, we explored a 1-step preparation of AB ring fragment **6** (Scheme 3). Initial attempts to transform commercially available 2-chloro-3-quinolinecarboxaldehyde (**8**) into iodide **6** using a literature procedure[9] (NaI, TMSCl, $(HMe_2Si)_2O$, CH_3CN) for this type of conversion were unsuccessful. Finally, it was found that

(5) (a) Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971. (b) Comins, D. L.; Hong, H.; Jianhua, G. *Tetrahedron Lett.* **1994**, 35, 5331. (c) Comins, D. L.; Saha, J. K. *Tetrahedron Lett.* **1995**, *36*, 7995. (d) Comins, D. L.; Hong, H.; Saha, J. K.; Jianhua, G. *J. Org. Chem.* **1994**, *59*, 5120.

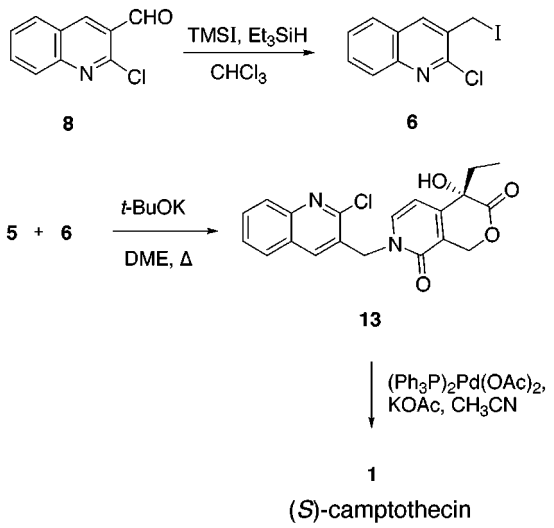
(6) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1988**, *29*, 773.

(7) (a) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1990**, *55*, 69. (b) For a review of α-amino alkoxide directed lithiations, see: Comins, D. L. *Synlett* **1992**, 615.

(8) TCC = *trans*-2-(α-cumyl)cyclohexyl: (a) (+)- and (−)-TCC alcohols are available from Aldrich Chemical Co. (b) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656 and references therein.

(9) Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett.* **1984**, *25*, 1103.

Scheme 3



a mixture of **8**, Et_3SiH, and TMSI in $CHCl_3$ (room temp, 12 h) effected the desired transformation to afford iodide **6** in 79% yield.[10] The completion of the CPT synthesis followed our earlier protocol.[5] The two fragments, **5** and **6**, were joined on treatment with *t*-BuOK in DME to provide compound **13**, which was recrystallized from MeOH to give an 81% yield of enantiopure material (>99% ee). As before, the C-ring was closed using a Heck reaction. Our reported conditions were modified to address the decreased reactivity of the quinoline C-2 halogen (Cl vs Br).[11] Treatment of **13** with $(PPh_3)_2Pd(OAc)_2$ (15%) and KOAc (2 equiv) in CH_3CN (100 °C) gave a 64% yield of (*S*)-camptothecin after recrystallization from 1,4-dioxane: mp 264−266 °C dec (lit.[1] 264−267 °C dec); $[\alpha]_D^{23}$ +45 (*c* 0.3, $CHCl_3$/MeOH 4:1) (lit.[12] +42 (*c* 0.51, $CHCl_3$/MeOH 4:1)). Our synthetic (*S*)-CPT was identical in every respect to authentic material.[13]

In summary, the shortest asymmetric synthesis of (*S*)-camptothecin to date has been achieved from two commercially available heterocycles. This 6-step synthesis is practical and should be amenable to the large-scale preparation of CPT analogues of medicinal importance.[14]

Acknowledgment. NMR and HRMS spectra were obtained at North Carolina State University instrumentation laboratories, which were established by grants from the North Carolina Biotechnology Center and the National Science Foundation (Grants CHE-9121380, CHE-9509532, and CHE-0078253).

Supporting Information Available: Experimental procedures for **1**,**5**−**7**, **10**, and **13** and characterization data for compounds **6**−**7**, **10**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The scope of this transformation is being studied and will be reported in due course.

(11) A 2-chloroquinoline has been used for a Heck reaction to generate a CPT analogue; see: Fang, F. G.; Bankston, D. D.; Huie, E. M.; Johnson, M. R.; Kang, M.-C.; LeHoullier, C. S.; Lewis, G. C.; Lovelace, T. C.; Lowery, M. W.; McDougald, D. L.; Meerholz, C. A.; Partridge, J. J.; Sharp, M. J.; Xie, S. *Tetrahedron* **1997**, *53*, 10953.

(12) Ejima, A.; Terasawa, H.; Sugimori, M.; Tagawa, H. *Tetrahedron Lett.* **1989**, *30*, 2639.

(13) The structure assigned to each new compound is in accordance with its IR, ^1H NMR, and ^{13}C NMR spectra and elemental analysis or high-resolution mass spectra.

(14) Various substituted 2-chloroquinoline-3-carboxaldehydes are readily available via Vilsmeier−Haack cyclization of the corresponding acetanilides; see: (a) Meth-Cohn, O.; Narine, B.; Tarnowski, B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1520. (b) Ali, M. M.; Tasneem; Rajanna, K. C.; Saiprakash, P. K. *Synlett* **2001**, 251 and references therein.