Catalytic Enantioselective Synthesis of 20(S)-Camptothecin: A Practical Application of the Sharpless Asymmetric Dihydroxylation Reaction

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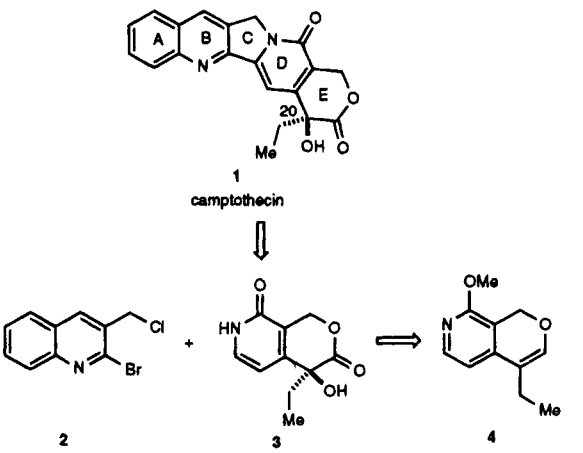
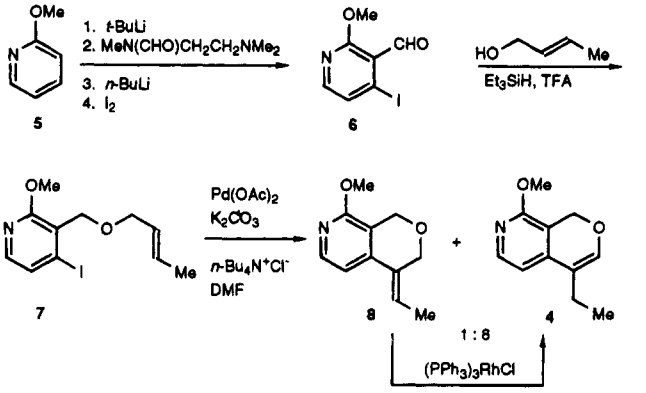
Summary: The first catalytic asymmetric route to 20-(*S*)-camptothecin was achieved, using as the key steps a tandem intramolecular Heck reaction/olefin isomerization process and a Sharpless asymmetric dihydroxylation (AD) reaction.

The novel structure and biological activity of 20(*S*)-camptothecin (**1**) have sustained a high level of interest in the total synthesis of this compound since its discovery by Wall and co-workers in 1966.[1-2] These efforts have played a crucial role in providing access to analogs with improved efficacy as potential cancer treatments.[3,4] In spite of these efforts, practical access to the biologically active 20(*S*)-isomer is still somewhat limited. Of the syntheses reported to date, two employ resolutions[5ab] and two utilize chiral auxiliaries.[5c,d] The synthesis reported by Comins *et al.*[5d] (Scheme 1) joins the AB- and DE-ring fragments (**2** and **3**, respectively) to give **1**. We were attracted by the overall convergence of Comins' route and its potential for application to the synthesis of therapeutically useful analogs of camptothecin (**1**). However, the required stoichiometric amounts of an expensive chiral auxiliary ((−)-8-phenylmenthol) used to selectively form the C.20 stereocenter limited practical access to large quantities of the key DE-ring fragment **3**. Recent developments by Sharpless and co-workers on the asymmetric dihydroxylation (AD) reaction offered a potential catalytic asymmetric synthesis solution (cf. **4** to **3**) to this problem.[6] Such an approach would be useful provided that two conditions could be met: (1) efficient construction of the required pyrido-fused cyclic enol ether substrate **4** and (2) high enantioselectivity in the subsequent AD reaction. In this paper we report the practical realization of these two goals and the first catalytic asymmetric synthesis of **3**.

Scheme 1



Scheme 2



The preparation of 4-iodo-3-formyl-2-methoxypyridine (**6**) in one pot from 2-methoxypyridine (**5**) was carried out according to the protocols of Comins.[5d] Reductive etherification of aldehyde **6** with crotyl alcohol, triethylsilane, and trifluoroacetic acid afforded, after distillation, the crotyl ether **7** (63%) (Scheme 2). An intramolecular Heck reaction was planned for formation of the key cyclic enol ether **4**.[7] We hoped that this process would be regioselective with respect to formation of the 6-membered ring while also resulting in placement of the double bond such that the presumably more stable enol ether isomer **4** would emerge.[8] In the event, heating compound **7** in *N,N*-dimethylformamide (DMF) at 90 °C in the presence of palladium(II) acetate (cat.), potassium carbonate, and tetra-*n*-butylammonium chloride for 24 h gave the cyclic olefins **4** and **8** in a ratio of 8:1. Fractional distillation of this crude mixture gave a 79% yield of **4** and **8** in a ratio of 11:1. Allylic ether **8** could be isomerized to enol ether **4** upon treatment with Wilkinsons' catalyst in *n*-PrOH at reflux.[9]

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(1) Isolation and structure determination: Wall, M. E.; Wani, M. C.; Cook, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888.

(2) For reviews on synthetic efforts in this field, see: (a) Curran, D. P.; Sisko, J.; Yeske, P. E.; Liu, H. *Pure Appl. Chem.* **1993**, *65*, 1153. (b) Cia, J. C.; Hutchinson, C. R. *Chem. Heterocycl. Compd.* **1983**, *25*, 753. (c) Cia, J. C.; Hutchinson, C. R. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. 21, p 101. (d) Hutchinson, C. R. *Tetrahedron* **1981**, *37*, 1047. (e) Schultz, A. G. *Chem. Rev.* **1973**, *73*, 385.

(3) For a recent review on the biological and clinical efficacy of camptothecin and analogs, see: Slichenmyer, W. J.; Rowinsky, E. K.; Donehower, R. C.; Kaufmann, S. H. *J. Nat. Cancer Inst.* **1993**, *85*, 271.

(4) See for example: Luzzio, M. J.; Besterman, J. M.; Evans, M. G.; Myers, P. L. European Patent Appl. 92203263.6. M. J. Luzzio *et al.* Novel Water-Soluble Camptothecin Analogs as Inhibitors of Topoisomerase I *84th Am. Assoc. Cancer Res.* **1993**, *34*, Abstract no. 1980.

(5) Syntheses of 20(*S*)-camptothecin: (a) Corey, E. J.; Crouse, D. N.; Anderson, J. E. *J. Org. Chem.* **1975**, *40*, 2140. (b) Wani, M. C.; Nicholas, A. 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*, 10972.

(6) For a recent review on asymmetric dihydroxylation, see: Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; VCH Publishers: New York, 1993.

(7) For a recent review of the Heck reaction, see: Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003.

(8) (a) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454. (b) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 6666.

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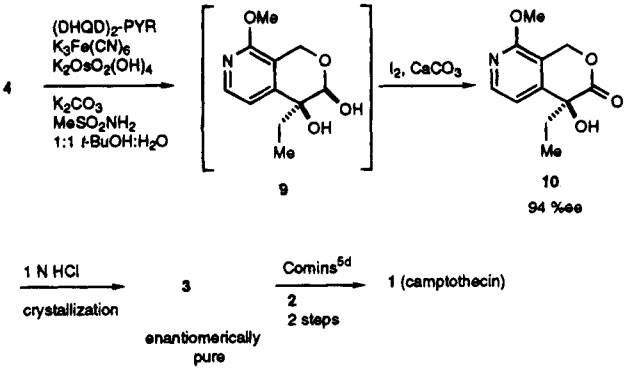
Substrate **4** was subjected to standard conditions used for the AD reaction (AD-mix-β, methanesulfonamide, *t*-BuOH, water, 0 °C, 24 h).[6] The resulting *cis*-diol **9** was oxidized *in situ* with iodine and calcium carbonate to provide hydroxyl actone **10**.[10] Disappointingly, the enantioselectivity for the dihydroxylation was found to be quite low (**10**, 26% ee).[11] The enantiomeric purity of **10** could be further enhanced through a recrystallization process.[12] Alternatively, enzymatic resolution of the racemic *cis*-diol precursor *rac*-**9** (prepared by nonasymmetric dihydroxylation of **4**) successfully distinguished the two enantiomers.[13] Although it was possible to obtain the desired isomer in enantiomerically pure fashion *via* these separation processes, a practical solution to the problem of stereoselectivity in the AD reaction still remained.

Toward this end, different chiral catalysts were examined. Fortunately, the recently disclosed $(DHQD)_2$–PYR ligand[14] gave a much more favorable result (**10**, 94% ee). Substrate **4** provides, to our knowledge, the most dramatic example of enhancement in stereoselectivity upon changing from the phthalazine to the pyrimidine ligands. Conversion of **10** to the corresponding pyridone **3** was accomplished by refluxing the substrate in 1 N hydrochloric acid (Scheme 3). The crystalline enantiomerically pure pyridone **3** was collected by filtration of the reaction mixture in 74% yield. Compound **3** was identical in all respects (^{1}H NMR, IR, mp, $[\alpha]_D$) with the intermediate produced in Comins' asymmetric synthesis of 20(*S*)-camptothecin (**1**).[5d,15]

Scheme 3



In summary, a 5-step catalytic asymmetric synthesis of the camptothecin DE-ring **3** has been described. The key steps in this sequence are an intramolecular Heck reaction/olefin isomerization process and a Sharpless asymmetric dihydroxylation reaction. Since Comins has previously recorded the high-yielding two-step conversion of **3** to 20(*S*)-camptothecin (**1**), this work constitutes an efficient formal synthesis of **1**. The chemistry described herein provides a practical route to 6-membered ring enol ethers and methods for their highly enantioselective transformation to α-hydroxy lactones.[16] In particular, large quantities of camptothecin analogs for further clinical development are now potentially accessible by total synthesis. Further applications of these reactions in the camptothecin series and toward the practical preparation of novel analogs are in progress and will be reported in due course.

Acknowledgment. We thank Professor Barry Sharpless (Scripps Institute) for a generous gift of $(DHQD)_2$–PYR. We also thank Professor Daniel Comins (North Carolina State University), Donald Bankston, Dr. M. C. Kang, and Dr. Matthew Sharp (Glaxo Inc.) for helpful discussions.

Supplementary Material Available: Experimental details for the preparation of **3**, **4**, **6**, **7** , **8**, and **10**, full spectroscopic and analytical characterization of **3**, **4**, **6**, **7**, **8**, and **10**, and selected NMR spectra and HPLC chromatograms (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehrmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102.

(10) Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1988**, *29*, 3205.

(11) The enantiomeric purity of **10** was determined using two methods: (1) ^{1}H NMR (400 MHz, $CDCl_3$) shift studies with Eu(hfc)$_3$; (2) chiral HPLC, Chiralcel-OD column 250 × 4.6 mm i.d. 2% ethanol/hexane, 26 °C, 1 mL/min λ = 276 nm, retention time **10** (14.92 min), *ent*-**10** (16.26 min).

(12) The enantiomeric purity could be enhanced via a recrystallization process. Thus, a 1.7:1 mixture of **10** and *ent*-**10** was recrystallized from *tert*-butyl methyl ether to give a 70% yield of crystalline *rac*-**10** (mp 103–104 °C). The mother liquor was concentrated to give a 27% yield of an amber oil which was enantiomerically enriched **10** (>95% ee).

(13) Selective acetylation of the undesired *cis*-diol could be accomplished using vinyl acetate and L-1754 lipase from *C. Cylindracea*. The desired *cis*-diol was obtained in 85% ee.

(14) $(DHQD)_2$–PYR is reported to be an improved ligand for the AD of monosubstituted olefins: Crispino, G. A.; Jeong, K.-S.; Kolb, H. C., Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.

(15) The enantiomeric purity for **3** was determined using chiral HPLC: Chiralcel-OD column 250 × 4.6 mm i.d. 10% ethanol/hexane, 26 °C, 1 mL/min λ = 300 nm, retention time **3** (32.2 min), *ent*-**3** (25.1 min).

(16) The same sequence of reactions described herein for 2-methoxypyridine have been applied to 6-chloro-2-methoxypyridine leading to an efficient synthesis of the "chloro"-DE-ring which is converted to **3** by hydrogenolysis.[5d]