Synthesis of Optically Active α-Hydroxy Lactones by Sharpless Asymmetric Dihydroxylations of Ketene Acetals, Enol Ethers, and Ene Lactones

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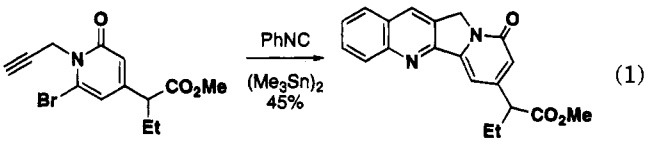
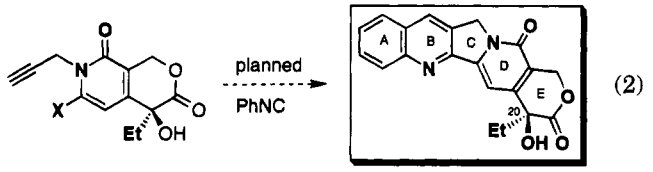
Summary: Three different AD routes to optically active α-hydroxy lactones of good to excellent optical purity are reported. The substrates for the AD reaction are endocyclic ketene acetals, endocyclic enol ethers, and exocyclic α,β-unsaturated lactones.

Compounds in the camptothecin family of pentacyclic alkaloids are currently among the most exciting leads in cancer chemotherapy.[1] Camptothecin itself (**1**) is a highly active, but insoluble, compound. Several synthetic analogs bearing groups on the A and B rings that confer modest water solubilities are now in clinical trials.[1] The excitement generated in medicinal chemistry has rekindled synthetic interest in the camptothecin class of compounds, and three new[2ab] or significantly improved[2c] total syntheses have recently appeared. Our recently reported eight-step synthesis of racemic camptothecin[2a] features the union of **2** and phenyl isonitrile by a radical annulation (eq 1). Though this route to **3** is short and



(1)

2 **3** precursor of (±)-camptothecin



(2)

4a X = Br
4b X = Cl

(20*S*)-camptothecin **1**

efficient, the first generation synthesis suffers because the conversion of **3** to camptothecin occurs in poor yield and produces a racemic mixture. We are currently pursuing a modified route to solve these problems, as shown in eq 2. Central to this route is the synthesis of optically active bromo hydroxy lactone **4a** or a close relative. Chloride **4b** is similar to a key intermediate in the efficient Comins synthesis, and it is already available in optically active form through the use of a chiral auxiliary.[2b]

With the ultimate goal of preparing optically active α-hydroxy lactones in the camptothecin family, we undertook a series of model studies applying the Sharpless catalytic asymmetric dihydroxylation (AD)[3,4] reaction to the synthesis of some simple α-hydroxy lactones. We now report the successful identification of three different routes to optically active α-hydroxy lactones of good to excellent optical purity through AD reactions of endocyclic ketene acetals, endocyclic enol ethers, and exocyclic α,β-unsaturated lactones. Though these three classes of alkenes are new to the AD, precedents from the Sharpless group[5] suggested that all three might be viable substrates. In the accompanying paper, Fang and coworkers[6] describe a practical asymmetric synthesis of camptothecin that incorporates an AD reaction of an enol ether.

Much of our model work has centered on developing routes to the simple benzo-fused lactone **7**. We first investigated a direct approach to **7** through ketene acetal derivatives of **5** (eq 3, Table 1). Silylation of **5** with *tert*-butyldimethylsilyl triflate or triisopropylsilyl triflate in the presence of triethylamine provided ketene acetals **6a** and **6b**.[7] Oxidation of **6a** and **6b** by the standard procedure with commercially available AD-mix-β (0.2% osmium, 1% $(DHQD)_2$–PHAL ligand[3c]) was very slow, but acceptable rates (24 h at 0 °C) were obtained by fortifying the AD-mix-β with up to 0.5% osmium and 2.5% ligand.[5b,c] After workup, we isolated 67–70% yields of hydroxy lactone **7**;[8] however, the enantiomeric excesses (as determined by $Eu(hfc)_3$-induced shifts in the ^1H NMR spectra) were only about 40% starting from **5a** and 30% starting from **5b**. Improved ee's were obtained with enol ester derivatives **6c** and **6d**, which were prepared by standard acylation procedures (Et_3N, DMAP, CH_2Cl_2)

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(4) Review of asymmetric dihydroxylation: Lohray, B. B. *Tetrahedron Asymmetry* **1992**, *3*, 1317.

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(8) For good yields of **7**, it is crucial to acidify the aqueous phase prior to extraction. Presumably, the basic phase contains the salt of the open hydroxy acid derivative of **7**. The following data were obtained on a 78% ee sample of **7R**: ^1H NMR δ 0.96 (t, J = 7.3 Hz, 3 H), 1.79 (m, 2 H), 3.71 (s, 1 H), 5.29 (d, J = 14.5 Hz, 1 H), 5.53 (d, J = 14.5 Hz, 1 H), 7.14 (d, J = 7.4 Hz, 1 H), 7.17 (d, J = 7.4 Hz, 1 H), 7.33 (dd, J = 7.4, 7.4 Hz, 1 H), 7.64 (d, J = 7.4 Hz, 1 H); ^{13}C NMR δ 7.55, 31.09, 70.04, 73.53, 124.00, 124.94, 127.55, 128.56, 136.81, 175.14; IR (neat, cm^{-1}) 3486, 2975, 2936, 1738, 1489, 1464, 1393, 1270, 1237, 1181, 1144, 1034, 997, 760; exact mass calcd for $C_9H_7O_3$ ($M - CH_2CH_3$) 163.0395, found 163.0394; 78% ee by NMR shift experiment; $[\alpha]^{20}_D = -48.3$ (CH_2Cl_2, c = 0.183).

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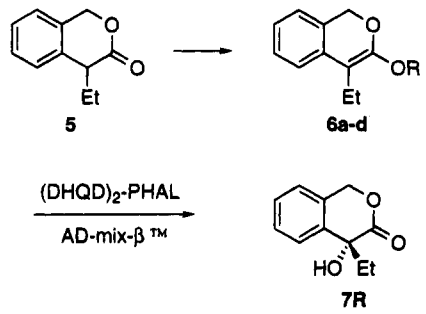
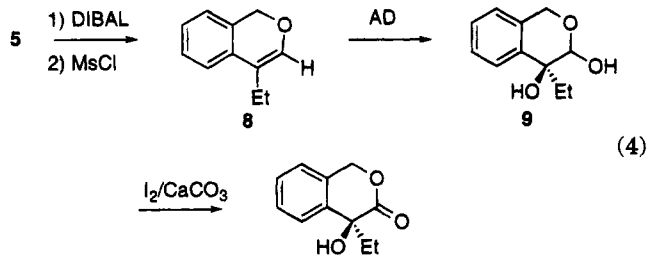
Table 1



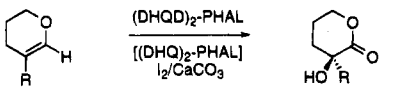
entry	R	**7R**, ee (%)	yield (%)
6a	$Si(Me)_2{}^tBu$	40	70
6b	$Si(^iPr)_3$	30	67
6c	COPh	65	82
6d	$COC(Me)_3$	78	100
6d[a]	$COC(Me)_3$	67	73

[a] $(DHQD)_2$-PYR ligand used.

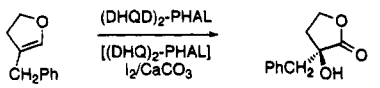
Table 2



ligand	product	ee (%)	yield (%)
$(DHQD)_2$–PHAL	**7S**	74	90
$(DHQD)_2$–PYR	**7S**	91	68
$(DHQ)_2$–PHAL	**7R**	63	84
$(DHQ)_2$–PYR	**7R**	78	69



R = Et 78% ee, 70% yield [83% ee, 69% yield]
R = CH_2Ph 72% ee, 81% yield [76% ee, 81% yield]

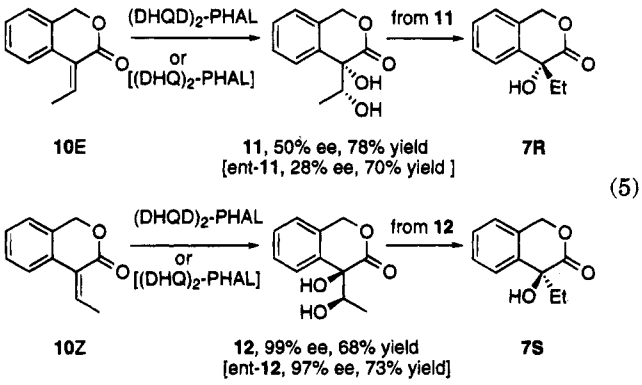


50% ee, 87% yield [48% ee, 87% yield]

with benzoyl chloride (47% yield of **6c**) and pivaloyl chloride (92% yield of **6d**). Hydroxylation of **6c** with the fortified AD-mix-β provided **7R** in 82% yield and 65% ee while hydroxylation of **6d** provided a near-quantitative yield of **7R** in 78% ee. Oxidation of **6d** with the recently introduced $(DHQD)_2$–PYR ligand[3f] gave **7R** in a reduced ee of 67%. The pivalate **6d** looks especially promising in view of the good ee and the excellent yields that were obtained in both steps. We suspect that the high yields obtained with the pivalate relative to the other substrates are due to its resistance to hydrolysis under the reaction conditions.[9]

Since trisubstituted alkenes are generally more reactive and give better ee's in the Sharpless AD reaction than their tetrasubstituted relatives,[3,5] we developed a second approach to **7** through cyclic enol ether **8** (eq 4, Table 2). By applying the Sharpless model to these substrates,[3c] we anticipated a reversal in enantioselectivity of **8** relative to **6**. The enol ether was prepared by the reduction of **5** with DIBAL and dehydration of the resulting lactol via its mesylate. Oxidation of **8** with the fortified AD-mix-β smoothly provided a crystalline hydroxyl lactol **9**, which was immediately oxidized with $I_2/CaCO_3$.[10] Through this two-step procedure, we obtained a 70% overall yield of a mixture now rich in **7S** (74% ee). We also subjected three simple cyclic enol ethers to this two-step procedure, and the results are summarized at the bottom of Table 2. The structures shown are those resulting from oxidation with AD-mix-β [$(DHQD)_2$–PHAL]. Each oxidation was also conducted with AD-mix-α [$(DHQ)_2$–PHAL] to provide mixtures rich in the enantiomeric products, and the results of these experiments are in brackets. Oxidation of **8** with the $(DHQD)_2$–PYR ligand[3f] produced **7S** in an improved ee of 91%, and its oxidation with the pseudoenantiomeric $(DHQ)_2$–PYR ligand (78% ee) was better than the $(DHQ)_2$–PHAL counterpart (63% ee). From these few experiments, it appears that 6-membered enol ethers consistently produce good ees (63–91%) while 5-membered enol ethers give moderate ees (48–50%). The PYR ligand is superior to the PHAL ligand in AD-mix, and yields are universally good (69–90%).

We have also investigated a third approach to **7** starting from unsaturated lactones **10E** and **10Z** (eq 5).



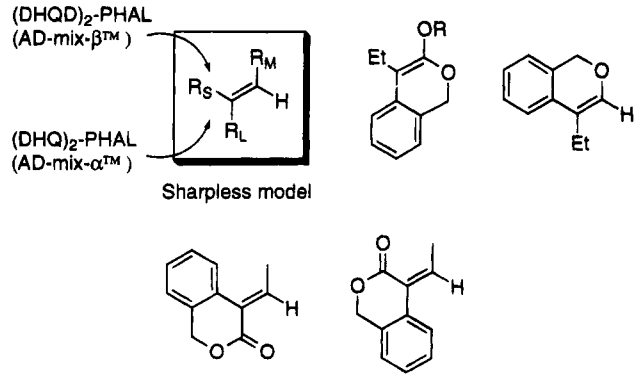
That conjugated alkenes often give excellent ees[3,5] makes this approach attractive, but added steps are required to remove the unwanted secondary hydroxy group that is introduced. The reaction of **10E** with AD-mix-α was disappointing and provided diol *ent*-**11** in 70% yield but with 28% ee (as determined by formation of the mono-MTPA ester of the secondary alcohol). AD-mix-β gave a somewhat improved ee (50%) for formation of **11**. In contrast, oxidation of **10Z** provided diol **12** in 68% isolated yield with a 99% ee. By using AD-mix-α, we obtained the enantiomer of **12** in 97% ee and 73% yield.

Deoxygenation of **12** to form **7** was not straightforward. Attempts to form xanthates and related precursors for Barton–McCombie deoxygenations did not succeed. However, **12** could be converted to a secondary bromide by treating its derived secondary mesylate with $MgBr_2{\cdot}Et_2O$ (45%). Reduction of the bromide with tributyltin hydride then provided **7S** in 53% yield. Improvement of these steps would be required to make this a practical process.

The absolute stereochemistry of the major diol **7** produced in the oxidation of **10** was proven by securing an X-ray crystal structure of the major diastereomer produced upon monoacylation of the diol *ent*-**11** with (*R*)-

(9) Attempts to hydroxlate the TMS enol ether of **6** provided only the hydrolized lactone **5**.

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



(−)-*O*-acetylmandelic acid.[11,12] Absolute configurations of the monocyclic hydroxy lactones (eq 4, Table 2) were assigned by analogy. The Sharpless model[3c] for predicting the sense and degree of asymmetric induction fares well with these substrates, as shown in Figure 1. For the tetrasubstituted ketene acetals, the model predicts the correct products if the most sterically demanding position (H) is occupied by the ring oxygen. For the three classes of trisubstituted alkenes, the predictions of the model are unambiguously correct. An especially powerful feature of the model is the correct prediction that **10Z** should provide higher selectivity than **10E**.

These results suggest that all three ADH approaches may be generally useful for the synthesis of optically active α-hydroxy lactones. We also believe that there is room for improvement in both the ees and yields of some of these hydroxylations; to date, we have made no efforts at optimization.

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Supplementary Material Available: Full experimental details and compound characterizations (7 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.

(11) Formation of MTPA esters: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(12) We thank Dr. S. V. Gieb for solving this crystal structure. The author has deposted atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.