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An Improved Preparation of Highly Enantiomerically Enriched (*R*)-(+)-4-*tert*-Butyldimethylsiloxy-2-cyclopenten-1-one.

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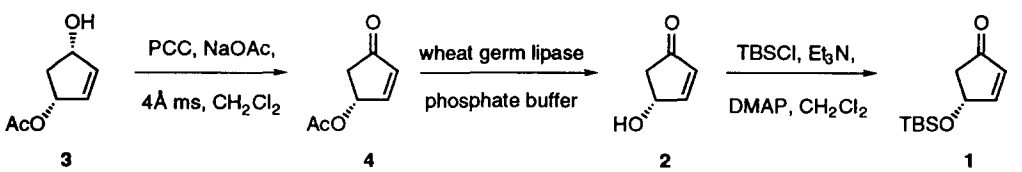
Abstract: A convenient procedure for the preparation of the title compound of ≥99% ee is presented as well as simple analytical methods for the determination of the optical purity of the product and intermediates in the sequence. Copyright © 1996 Elsevier Science Ltd

The chiral building block (*R*)-(+)-4-*tert*-butyldimethylsiloxy-2-cyclopenten-1-one ((+)-**1**) has proven to be a valuable precursor for the synthesis of prostaglandins and other important biologically active substances in optically active form.[1] As a consequence, numerous asymmetric syntheses of (+)-**1**[2] as well as other derivatives of (*R*)-(+)-4-hydroxy-2-cyclopenten-1-one ((+)-**2**)[3] have been developed. The most widely employed procedure for the synthesis of (+)-**1** is summarized in Scheme I and has recently appeared in detailed form as a procedure in *Organic Syntheses*.[2i] This protocol involves three chemical steps from the highly enantiomerically enriched starting material (1*R*,3*S*)-(+)-4-hydroxy-2-cyclopentenyl acetate ((+)-**3**). The preparation of (+)-**3** of ≥99% ee by the enantioselective hydrolysis of *cis*-3,5-diacetoxycyclopentene has also appeared as an *Organic Syntheses* procedure, accompanying the reported preparation of (+)-**1**.[4]

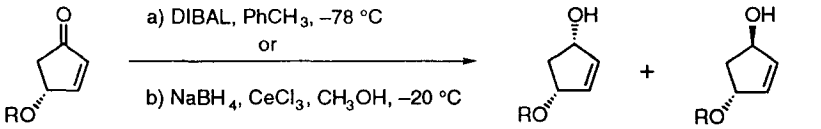
In the course of synthetic studies of the antitumor agent neocarzinostatin chromophore, we have employed (+)-**1** as a key building block. Although we were successful in preparing gram-quantities of (+)-**1** employing the published procedure,[2i] aspects of this protocol were found to be inconvenient for rapid and large-scale material throughput. In addition, we found evidence that this route produced (+)-**1** with eroded optical purity (vide infra).



Scheme I

The most inconvenient step in the published protocol is the hydrolysis of (*R*)-(+)-4-acetoxy-2-cyclopenten-1-one ((+)-**4**) to (+)-**2** using wheat germ lipase as a catalyst. This step requires 7 days to conduct the reaction, and 3 days to isolate the product by continuous extraction with a large volume of ethyl acetate. The purification of the final product ((+)-**1**) is also laborious, involving flash column chromatography, short-path distillation, and low-temperature recrystallization from pentane.

In an initial effort to simplify the procedure, we modified the published protocol for the purification of (+)-**1** by omitting the low-temperature recrystallization step. Residual *tert*-butyldimethylsilanol from the silylation reaction (**2** → **1**) was removed by vacuum distillation, and the distillation residue was purified by flash column chromatography (20% ethyl acetate in hexanes) affording (+)-**1** as a low-melting white solid in 72% yield (from **4**). When we employed this material in synthetic studies of neocarzinostatin chromophore, results obtained from a step involving the coupling of a component derived from (+)-**1** with a chiral acetylide anion suggested that the synthetic (+)-**1** we had used was not optically pure. This was established unequivocally by reducing (+)-**1** with diisobutylaluminum hydride (DIBAL) in toluene at –78 °C to afford a diastereomeric mixture of the alcohols **5a** and **5b**, in which the former predominated (Scheme II). Isomer **5a** was separated and transformed into the corresponding Mosher ester derivative using the (*S*)-(+)-Mosher acid chloride.[5] Capillary gas chromatographic (gc) analysis[6] of the Mosher ester showed it to be of 88% de. We show below that this analytical method proceeds without detectable racemization in (+)-**1** or any intermediate and, therefore, that our sample of synthetic (+)-**1** was 88% ee. We hasten to emphasize that this sample of (+)-**1** was obtained using a modification of the published procedure. It is reasonable, if not likely, that the low-temperature recrystallization step we omitted would have increased the optical purity of the final product; we did not explore this. Rather, we sought to determine the source of racemization in our synthetic (+)-**1**.



1 R = TBS
4 R = Ac

5a R = TBS
6a R = Ac

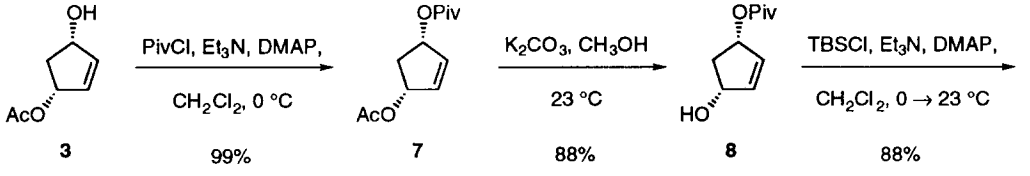
5b R = TBS
6b R = Ac

Scheme II

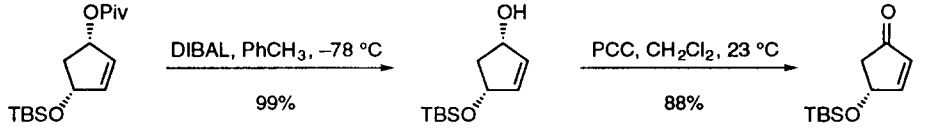
We were able to exclude the oxidation of (+)-**3** to (+)-**4** as the problematic step by reducing (+)-**4** with sodium borohydride in the presence of cerium(III) chloride to furnish the alcohols **6a** and **6b**.[8] The major diastereomer (**6a**) was separated and transformed into the corresponding Mosher ester derivative using (*S*)-(+)-Mosher acid chloride.[5] Capillary gas chromatography showed this Mosher ester to have a de of ≥99%.[6] This was an important finding, for it demonstrated that the rate of internal acetate migration within **6a** (leading to racemization) was indetectably slow, and established the accuracy of the analytical method.[6] This observation was also critical to the development of our improved procedure (Scheme III below). We were unable to determine unequivocally which of the two remaining steps in the sequence, the lipase-catalyzed hydrolysis of (+)-**4** or the subsequent silylation step (or both), was leading to racemization. The ee of the product of lipase-catalyzed hydrolysis, (+)-**2**, could not be determined directly. In an indirect method, a Mosher ester derivative of (+)-**2** was prepared, as above, and was found to be approxiamtely 90% de by ^{1}H NMR analysis. Although this suggests that the racemization occurred in the lipase-catalyzed hydrolysis step, we could not rule out the possibility that the erosion in ee occurred during the Mosher esterification reaction. There was no doubt, however, that detectable racemization was occurring in one or both of the final steps. This, coupled with the

time-consuming and laborious procedure for the lipase-catalyzed hydrolysis step, led us to develop an alternative synthesis of (+)-**1** that involved neither of the final steps of the published route.[2i]

Scheme III outlines an improved synthesis of (+)-**1** that provides product of ≥99% ee and is easily conducted on large scale. Like the previous route, the starting material is (+)-**3**, readily available in quantity and in ≥99% ee. Treatment of (+)-**3** with pivaloyl chloride (1.25 equiv), triethylamine (5.0 equiv), and 4-dimethylaminopyridine (DMAP, 0.5 equiv) led to the formation of pivaloate ester **7** ($[\alpha]_D^{20} = -17.24°$ (*c* 3.40, CH_2Cl_2)) in 99% yield. Selective hydrolysis of the acetate ester within **7** was accomplished using potassium carbonate (1.0 equiv) in methanol to afford the hydroxy ester **8** ($[\alpha]_D^{20} = -65.09°$ (*c* 2.79, CH_2Cl_2)) in 88% yield and ≥99% ee, as determined by gc analysis[6] of the corresponding Mosher ester. Addition of *tert*-butyldimethylsilyl chloride (2.0 equiv), triethylamine (5.0 equiv) and DMAP (0.5 equiv) to **8** produced the corresponding silyl ether **9** as a white solid (mp 64-66 °C, $[\alpha]_D^{20} = -10.11°$ (*c* 1.82, CH_2Cl_2)), in 88% yield.[9] The pivaloate group of **9** was cleaved with DIBAL (2.0 equiv) in toluene at –78 °C affording the alcohol **5a** ($[\alpha]_D^{20} = +24.29°$ (*c* 2.47, CH_2Cl_2)) in quantitative yield and ≥99% ee as determined by gc analysis[6] of the corresponding Mosher ester derivative. The latter observation established that intramolecular migration of the *tert*-butyldimethylsilyl group of **5a**, like the acetate group of **6a**, is not detectable under these conditions. Oxidation of **5a** with pyridinium chlorochromate (1.7 equiv) in dichloromethane[10] gave (+)-**1** (mp 30-31 °C, $[\alpha]_D^{20} = +68.00°$ (*c* 1.00, CH_3OH)[11]) in 88% yield after purification by flash chromatography. Reduction of (+)-**1** prepared in this way with DIBAL, as above, and Mosher esterification of the resulting alcohol **5a** afforded a Mosher ester of ≥99% de, as determined by gc analysis.[6] To confirm the result, the minor diastereomer in the reduction, the *trans*-alcohol **5b**, was also transformed into its Mosher ester derivative. The resulting Mosher ester was shown to be ≥99% de by gc analysis. These results establish that synthetic (+)-**1** produced by the new route is of ≥99% ee and that the analytical method used proceeds without enantiomerization of **1** or any derivative in the sequence.



3 — 99% — 7 — 88% — 8 — 88%



9 — 99% — 5a — 88% — 1

Scheme III

We have found the route depicted in Scheme III to be highly effective for preparing large quantities (≥20 g) of (+)-1 of ≥99% ee. Although the new route is two steps longer than the previously published method,[2i] we have found it to be, by far, the faster preparation. The overall yield of (+)-1 prepared by the new route is 68% from the known compound (+)-3, compared to the previously reported yield of 32% from the same starting material.[2i] We believe that this new procedure offers a simple and reliable method for the preparation of (+)-1 of ≥99% ee.

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