Enantioselective Total Synthesis of (+)-Cassiol

Krastina V. Petrova, Justin T. Mohr, and Brian M. Stoltz


Downloaded from http://pubs.acs.org on January 30, 2009

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 1 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML
Enantioselective Total Synthesis of (+)-Cassiol

Krastina V. Petrova, Justin T. Mohr, and Brian M. Stoltz*

The Arnold and Mabel Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 East California Boulevard, MC 164-30, Pasadena, California 91125

stoltz@caltech.edu

Received October 19, 2008

ABSTRACT

An enantioselective total synthesis of (+)-cassiol is reported. The complex derived from Pd$_2$(pmdba)$_3$ and enantiopure $t$-BuPHOX ligand catalyzes enantioconvergent decarboxylative alkylation to generate the quaternary carbon stereocenter at an early stage. The overall synthetic strategy involves a convergent late-stage coupling of two fragments. The synthesis features a longest linear sequence of eight steps.

In 1988, Fukaya reported the isolation of (−)-cassioside (2) (Figure 1) from the stem bark of Cinnamomum cassia Blume. This glycosylated sesquiterpenoid exhibited potent antiulcerogenic activity in rats. The aglycon of (−)-cassioside, (+)-cassiol (1), demonstrated even stronger antiulcerogenic activity than observed with the glycosylated precursor. Given this useful biological property, (+)-cassiol (1) has attracted a great deal of attention from synthetic laboratories.2 Herein, we report an expedient enantioselective synthesis of (+)-cassiol with a longest linear sequence of eight steps.

A principal challenge to the synthesis of (+)-cassiol (1) is the presence of an all-carbon quaternary stereocenter.3 Several total syntheses of cassiol have been reported; however, most have relied on chiral pool starting materials or chiral auxiliaries.4,5 Few of these syntheses addressed the challenge of catalytic enantioselective quaternary carbon stereocenter generation. For example, successful catalytic enantioselective approaches have utilized Diels–Alder,6 intramolecular alkylidene insertion,7 and enzymatic8 reactions to form the quaternary carbon. We envisioned a different strategy9 wherein the key quaternary stereocenter would be installed through an enantioselective Pd-catalyzed allylic alkylation method recently developed in our laboratories.10 Our plan consisted of coupling two complex pieces (3 and...
Subsequent position-selective alkylation with iodomethane provided racemic \(-\)-ketoster 7 in 78% overall yield from 4. In the presence of the catalyst complex derived from Pd(O)(pmdba)\(_2\) \(\rightarrow\) 13:1 mixture by 'H NMR. For a review of the development of the enantioselective Tsuji alkylation in our laboratory and others, see: (d) Mohr, J. T.; Stoltz, B. M. "Asymmetric Synlett 2007, 2, 1476–1491.

---


(5) One total synthesis of (+)-cassiol (2) using a chiral auxiliary has also been reported, see: Boeckman, R. K., Jr.; Liu, Y. J. Org. Chem. 1996, 61, 7984–7985.
reasoned that the smaller steric size of this ligand might improve the rate of oxidation in our system. This proved to be the case, and dihydroxylation proceeded smoothly with no evidence of undesired vinylogous thioester oxidation.\(^{20}\) Immediate exposure of the crude diol to Pb(OAc)\(_4\) furnished pure aldehyde (\(-\))\(_{11}\) in 70\% overall yield for the two oxidative transformations.

Treatment of aldehyde (\(-\))\(_{11}\) with NaBH\(_4\) or NaBH(OAc)\(_3\) resulted in rapid reduction of both carbonyl groups present in the substrate. Fortunately, use of the bulkier reducing agent Li(O-t-Bu)\(_3\)AlH circumvented the problem of overreduction and provided the desired alcohol (\(-\))\(_3\) in good yield. Chiral HPLC analysis of (\(-\))\(_3\) indicated that no significant erosion of enantiomeric purity had occurred over the course of these steps.

Turning our attention to the synthesis of vinyl iodide 5, we prepared alcohol 6 in four known steps from diethyl malonate.\(^{13}\) Catalytic oxidation of alcohol 6 to the corresponding aldehyde was accomplished with TEMPO and PhI(OAc)\(_2\) as the stoichiometric co-oxidant (Scheme 3).\(^{21}\)

\[ \text{Scheme 3. Synthesis of Vinyl Iodide 5}^a \]

\[ \begin{align*}
\text{EtO} & \quad \text{EtO} \quad \text{EtO} \\
12 & \rightarrow \text{Ref 12} \rightarrow \text{Tempo} \rightarrow \text{PhI(OAc)}_2 \rightarrow \text{EtO}
\end{align*} \]

\(^a\) TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl

Takai olefination\(^{22}\) of the crude aldehyde to stereoselectively introduce the alkene functionality yielded vinyl iodide 5 in a 5:1 E/Z ratio.

In the final step of the synthesis (Scheme 4), lithium—halogen exchange of vinyl iodide 5 (2 equiv) through exposure to t-BuLi (4.25 equiv) in diethyl ether furnished vinyllithium 13. Addition of a solution of alcohol (\(-\))\(_3\) (1 equiv) to the solution of organolithium 13 and subsequent acid-catalyzed rearrangement and hydrolysis yielded (\(+\))-cassiol (1).\(^{7}\) The spectroscopic data (\(^1\)H NMR, \(^{13}\)C NMR, IR, HRMS, optical rotation) were identical to the reported data for natural 1.

\[ \text{Scheme 4. Preparation of (\(+\))-Cassiol (1)} \]

In summary, we report a brief and convergent total synthesis of the antiulcerogenic natural product (\(+\))-cassiol. Our route requires eight linear steps from vinylogous ester 4 and proceeds in 12\% overall yield. Employing our recently developed enolate alkylation technology, the key quaternary carbon stereocenter was generated at an early stage. The versatile reactivity of the allyl group enabled installation of the hydroxymethylene unit present in the natural product through chemoselective oxidation and reduction reactions. Late-stage installation of the diol side chain via Stork—Danheiser-type addition/rearrangement completed the synthesis. Other synthetic efforts featuring enantioselective enolate functionalization reactions are underway.\(^{23}\)

**Acknowledgment.** We thank Samantha R. Levine and Michael R. Krouth (Caltech) for helpful discussions and experimental assistance. We thank the NIH-NIGMS (R01 GM080269-01), Caltech Amgen Scholars Program (undergraduate fellowship to K.V.P.), Eli Lilly (predoctoral fellowship to J.T.M.), Amgen, Bristol-Myers Squibb, Merck Research Laboratories, Abbott Laboratories, Boehringer-Ingelheim, and Caltech for financial support.

**Supporting Information Available:** Experimental details and NMR spectra of all intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

\(^{20}\) Other amine additives (DMPA, quinuclidine) were not as effective as DABCO.
