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Enantioselective Total Synthesis of (+)-Cassiol

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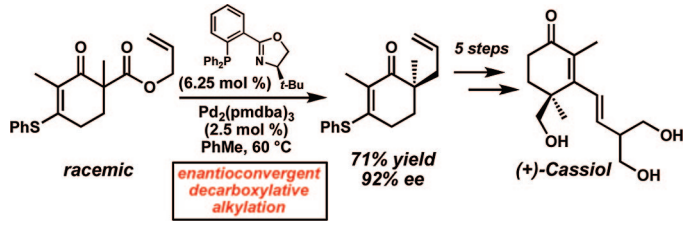
ABSTRACT



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.[1] 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 alkylidine insertion,[7] and enzymatic[8] reactions to form the quaternary carbon. We envisioned a different strategy[9] 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

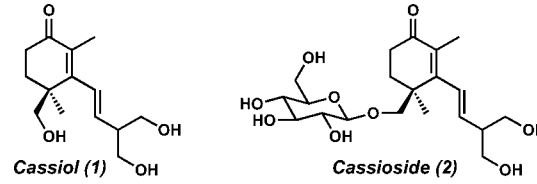


Figure 1. (+)-Cassiol (**1**) and (−)-cassioside (**2**).

(1) Shiraga, Y.; Okano, K.; Akira, T.; Fukaya, C.; Yokoyama, K.; Tanaka, S.; Fukui, H.; Tabata, M. *Tetrahedron* **1988**, *44*, 4703–4711.

(2) For an overview of previous syntheses of (+)-cassiol, see: Colombo, M. I.; Rúveda, E. A. *J. Braz. Chem. Soc.* **1998**, *9*, 303–312.

(3) For recent reviews of the synthesis of quaternary stereocenters, see: (a) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, *36*, 5969–5994. (b) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396. (c) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley: Weinheim, 2005. (d) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363–5367. (e) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105–10146.

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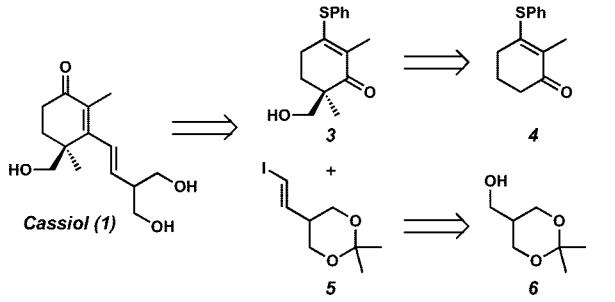
5, Scheme 1) in the final step of the synthesis through a Stork−Danheiser-type addition/rearrangement reaction.[11]

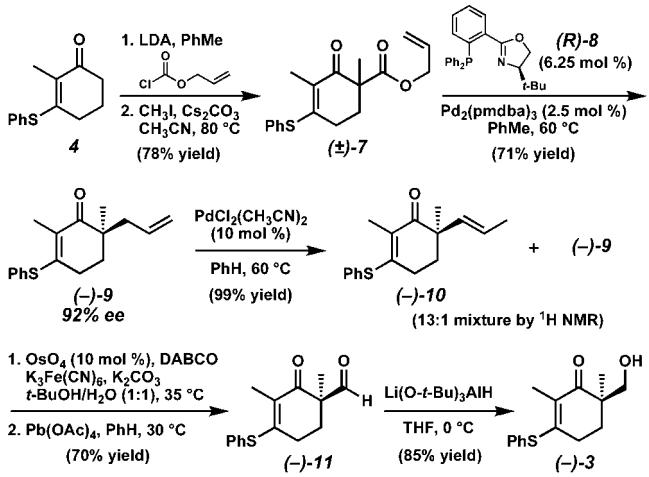
Scheme 1. Retrosynthetic Analysis of (+)-Cassiol (**1**)



Precursors **3** and **5** would in turn be available from known vinylogous thioester **4**[12] and primary alcohol **6**,[13] respectively.

Our synthesis commenced with the deprotonation of vinylogous thioester **4** with LDA and acylation of the resulting enolate with allyl chloroformate (Scheme 2).

Scheme 2. Enantioselective Synthesis of Alcohol (−)-**3**[a]



[a] pmdba = bis(4-methoxybenzylidene)acetone; DABCO = 1,4-diazabicyclo[2.2.2]octane.

Subsequent position-selective alkylation with iodomethane provided racemic β-ketoester **7** in 78% overall yield from **4**. In the presence of the catalyst complex derived from $Pd_2(pmdba)_3$ and (*R*)-*t*-BuPHOX (**8**),[14] β-ketoester (±)-**7** was readily transformed into allyl ketone (−)-**9** in good yield and excellent enantiomeric excess.[12a] Isomerization of the terminal alkene occurred upon exposure to catalytic $PdCl_2(CH_3CN)_2$ in hot benzene, resulting in quantitative recovery of an inseparable 13:1 mixture of *E*-alkene **10** and starting material **9**.

In order to convert the propenyl side chain of **10** into a hydroxymethylene unit, we sought to carry out an oxidative olefin cleavage reaction. This transformation, however, proved challenging. Competing oxidative reactions of the thioester moiety appeared to occur rapidly under ozonolysis conditions. Modified Lemieux−Johnson conditions (OsO_4, $NaIO_4$, 2,6-lutidine, dioxane/water)[15] were also investigated but led to a complex mixture of products lacking the desired compound. Both Upjohn dihydroxylation (OsO_4, NMO, acetone)[16] and Sharpless asymmetric dihydroxylation conditions (AD-mix-α or AD-mix-β, *t*-BuOH/H_2O)[17] resulted in slow and only partial conversion to the desired diol product.

Confronted by these difficulties, we considered possible opportunities to improve reactivity for our system. We wished to take advantage of the well-precedented rate-acceleration of amine additives in osmium-catalyzed dihydroxylation reactions,[18] but we reasoned that the bulky chiral ligands employed in the Sharpless protocol might hamper reactivity toward our sterically encumbered, enantiomerically enriched olefin. Warren, Wyatt, and co-workers had found DABCO to be a convenient achiral ligand for nonenantioselective dihydroxylations,[19] and we

(4) For syntheses of (+)-cassiol using chiral auxiliaries, see: (a) Takemoto, T.; Fukaya, C.; Yokoyama, K. *Tetrahedron Lett.* **1989**, *30*, 723–724. (b) Irie, O.; Fujiwara, Y.; Neomoto, H.; Shishido, K. *Tetrahedron Lett.* **1996**, *37*, 9229–9232. (c) Maiti, S.; Achari, B.; Banerjee, A. K. *Synlett* **1998**, 129–130. (d) Momose, T.; Toyooka, N.; Nishio, M.; Shinoda, H.; Fujii, H.; Yanagino, H. *Heterocycles* **1999**, *51*, 1321–1343. (e) Colombo, M. I.; Zinczuk, J.; Mischne, M. P.; Rúveda, E. A. *Tetrahedron: Asymmetry* **2001**, *12*, 1251–1253. (f) Shen, X.; Wu, Y.-K.; Zhang, F. *Chin. J. Chem.* **2002**, *20*, 1439–1444. (g) Colombo, M. I.; Zinczuk, J.; Bohn, M. L.; Rúveda, E. A. *Tetrahedron: Asymmetry* **2003**, *14*, 717–725.

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(7) Taber, D. F.; Meagley, R. P.; Doren, D. J. *J. Org. Chem.* **1996**, *61*, 5723–5728, and references therein.

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(9) For a review of enantioselective methodologies inspired by target-directed synthesis, see: Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Nature* **2008**, *455*, 323–332.

(10) (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924–6927. (c) Seto, M.; Roizen, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6873–6876. For a review of the development of the enantioselective Tsuji allylation in our laboratory and others, see: (d) Mohr, J. T.; Stoltz, B. M. *Chem.−Asian J.* **2007**, *2*, 1476–1491.

(11) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775–1776.

(12) The use of a vinylogous thioester is important to the success of the subsequent enantioselective alkylation reaction, see: (a) Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 289–292. For the use of vinylogous thioesters in a related system and the preparation of **4**, see: (b) Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109–3112.

(13) Bates, H. A.; Farina, J.; Tong, M. *J. Org. Chem.* **1986**, *51*, 2637–2641.

(14) For the development of phosphinooxazoline (PHOX) ligands, see: (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345. (b) Williams, J. M. J. *Synlett* **1996**, 705–710.

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(16) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973–1976.

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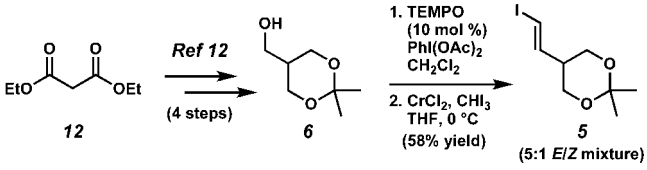
(19) Eames, J.; Mitchell, H. J.; Nelson, A.; O'Brien, P.; Warren, S.; Wyatt, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1095–1103.

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 $Li(O\text{-}t\text{-}Bu)_3AlH$ 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]

Scheme 3. Synthesis of Vinyl Iodide **5**[a]



[a] TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxy

Takai olefination[22] of the crude aldehyde to stereoselectively introduce the alkene functionality yielded vinyl iodide **5** in a 5:1 *E*/*Z* ratio.

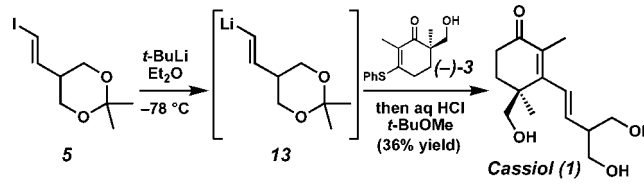
In the final step of the synthesis (Scheme 4), lithium−halogen exchange of vinyl iodide **5** (2 equiv) through exposure to *t*-BuLi (4.25 equiv) in diethyl ether furnished vinyllithium **13**. Addition of a solution of alcohol (−)-**3** (1 equiv) to the solution of organolithium **13** and subsequent acid-catalyzed rearrangement and hydrolysis yielded (+)-cassiol (**1**).[7] The spectroscopic data (^1H NMR, ^{13}C NMR, IR, HRMS, optical rotation) were identical to the reported data for natural **1**.

(20) Other amine additives (DMAP, quinuclidine) were not as effective as DABCO.

(21) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977.

(22) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.

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]

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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.

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(23) For other synthetic applications of this reaction from our laboratory, see: (a) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739. (b) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348–11349. (c) Behenna, D. C.; Stockdill, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4077–4080. (d) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810–811. (e) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2008**, *10*, 1039–1042. (f) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231. (g) Ref 10. (h) Ref 12a.