Enantioselective Synthesis of Imperanene via Enzymatic Asymmetrization of an Intermediary 1,3-Diol

ARTICLE *in* ORGANIC LETTERS · SEPTEMBER 2004

Impact Factor: 6.36 · DOI: 10.1021/ol048802c · Source: PubMed

ORGANIC LETTERS

2004
Vol. 6, No. 19
3297−3300

Enantioselective Synthesis of Imperanene via Enzymatic Asymmetrization of an Intermediary 1,3-Diol

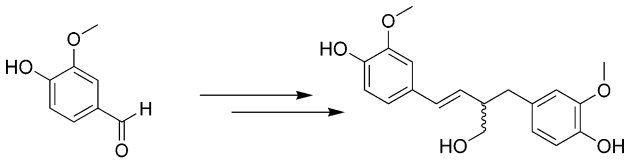
Jason A. Carr and Kirpal S. Bisht*

Department of Chemistry, University of South Florida, Tampa, Florida 33620

kbisht@cas.usf.edu

Received June 23, 2004

ABSTRACT

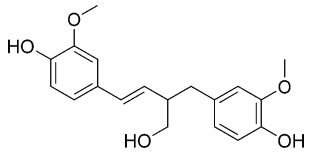


2 1

Using a chemoenzymatic synthetic strategy, (*S*)-imperanene and its (*R*)-enantiomer has been synthesized from vanillin in nine steps. The key step in the synthesis involves the use of *Pseudomonas cepacia* lipase (PS-30) to induce asymmetrization of the intermediary prochiral 1,3-diol in >97% ee.

Imperanene (**1**), a phenolic compound of the rare $C_6-C_4-C_6$ class of natural products, has been isolated from *Imperata cylindrical*[1] and possesses platelet aggregation inhibitory activity, making it a suitable candidate in the search for platelet aggregation inhibitors for the treatment of diseases such as stroke. Although imperanene was isolated as a single (+)-isomer, its absolute stereochemistry was not reported. Shattuck et al. have since established, through comparison of optical rotation data, the natural product to be the (*S*)-enantiomer.[2]

To date, four different synthetic approaches to imperanene have been reported. Shattuck et al.[2] employed the *R*AMP/*S*AMP chiral auxiliary method for asymmetric synthesis of both enantiomers of imperanene (**1**), whereas Eklund et al.[3] used a semisynthetic method for the synthesis of the (*R*)-



1

(−)-enantiomer starting from hydroxymatairesinol, a natural lignan from the Norway spruce. Doyle et al.[4] reported the synthesis of (*S*)-(+)-imperanene using an asymmetric chiral dirhodium(II) catalyst, and Davies et al.[5] established the efficient C−H activation of primary benzylic positions by means of rhodium carbenoid induced C−H insertion toward the synthesis of (+)-imperanene and (−)-conidendrin. Interestingly, all synthetic methods described above required the use of a chiral auxiliary or an organometallic catalyst. The semisynthetic method is very efficient but is not amenable to synthesis of the natural enantiomer or its structural analogues.

* To whom correspondence should be addressed. Fax: 813 974 3203. Tel: 813 974 0350.

(1) Matsunaga, K.; Shibuya, M.; Ohizumi Y. *J. Nat. Prod.* **1995**, *58*, 138.

(2) Shattuck, J. C.; Shreve, C. M.; Solomon, S. E. *Org. Lett.* **2001**, *3*, 3021.

(3) Eklund, P. C.; Riska, A. I.; Sjöholm, R. E. *J. Org. Chem*. **2002**, *67*, 7544.

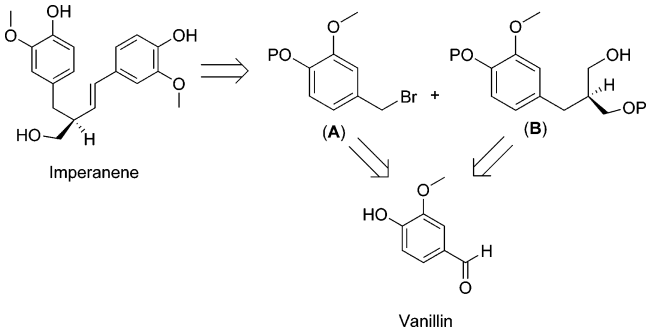
(4) Doyle, M. P.; Hu, W.; Valenzuela, M. V. *J. Org. Chem*. **2002**, *67*, 2954.

(5) Davies, H. M. L.; Jin, Q. *Tetrahedron: Asymmetry* **2003**, *14*, 941.

10.1021/ol048802c CCC: $27.50
Published on Web 08/19/2004

We envisaged a *divergent*−*convergent* synthetic strategy to imperanene starting from vanillin, which can be converted to a 1,3-diol (**8**) and the Wittig reagent (**6**) (Scheme 1).

Scheme 1[a]



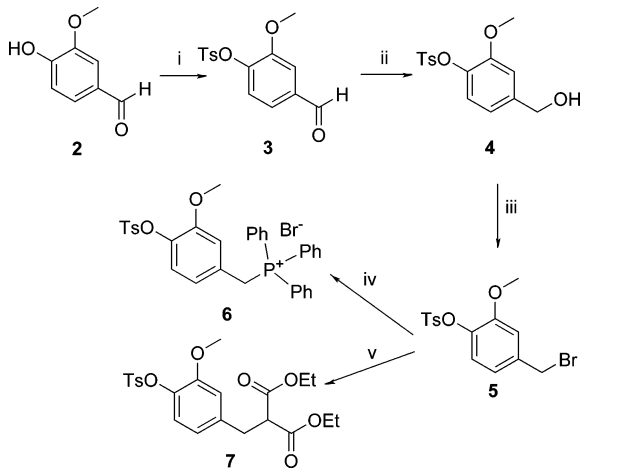
[a] P = protecting group.

The 1,3-diol is a key intermediate as it is prochiral and can be converted to an enantiomerically pure intermediate (**B**) in high yield. Thus diverging from a commercially inexpensive starting material (vanillin), the two pieces of the carbon skeleton of imperanene would be obtained. (*S*)-(+)-Imperanene would be readily derived through a Wittig coupling reaction of the aldehyde obtained from the (*S*)-enantiomer of **B** with the ylide generated from **A**. Similarly, the (*R*)-(−)-enantiomer would be derived from the (*R*)-enantiomer of **B**. The highlight of this strategy is the enantiocontrol exhibited by the biocatalyst during enzymatic acetylation of the prochiral 1,3-diol. Asymmetrization of prochiral diol intermediates is a very useful synthetic strategy because the maximum feasible yield upon lipase-catalyzed transformation is not limited to 50%, as happens when resolving racemates.[6]

Our choice of lipases as biocatalyst for the asymmetrization of the prochiral 1,3-diol was based upon their ability to assume a variety of conformations to accommodate substrates of varying sizes and complexities, providing one of the most useful and versatile biocatalytic methods in asymmetric synthesis and resolution of organic substrates with high efficiency and selectivity.[7] Furthermore, the lipase used herein was recyclable and was reused without significant loss in activity.

Our strategy for synthesis of imperanene began with the tosylation of vanillin (**2**) with tosyl chloride, affording the tosylated aldehyde (**3**) in 95% yield (Scheme 2). The choice of the protecting group turned out to be quite important.[8]

Scheme 2[a]



[a] Conditions: (i) tosyl chloride, K_2CO_3, acetone, reflux, 24 h, 95%; (ii) $NaBH_4$, MeOH, 0 °C, 8 h, 99%; (iii) PBr_3, ether, rt, 3 h, 98%; (iv) triphenylphosphine, toluene, reflux, 24 h, 97%; (v) diethylmalonate, NaH, 0 °C, 8 h, 88%.

Subsequent reduction with sodium borohydride yielded the alcohol (**4**) in 99% yield, which was readily brominated using phosphorus tribromide to afford the bromide (**5**) quantitatively.[9] It is important to note that the first four steps were readily amendable to large scales; high yields were achieved and no purifications by wet column chromatography were required. Purifications were easily accomplished by recrystallization.

The bromide (**5**) served as the intermediate for the divergent synthesis of the triphenylphosphonium bromide salt (**6**) (yield = 97%), which was synthesized by refluxing **5** with triphenylphosphine in toluene for 24 h and for the symmetrical alkylation of diethylmalonate affording the monoalkylated diethylmalonate (**7**) (yield = 88%), which was easily separated from the dialkylated product (5−10% yield) by column chromatography.

Reduction of the alkylated diethylmalonate (**7**) to the prochiral 1,3-diol (**8**) was accomplished using $NaBH_4$/LiCl (1:1.5) in methanol/ether (1:3) (Scheme 3).[10] The resulting diol was then selectively acylated using vinyl acetate as the acylating agent in the presence of lipase form *Pseudomonas cepacia* (Amano lipase PS-30). A systematic screening of a number of different lipases available in our laboratories led us to the most efficient route through use of the lipase PS-30.

The reaction gave the (*R*)-(+)-monoacetate (**9**) in good yield with high enantioselectivity.[11] The enantiopurity of the product acetate (**9**) was calculated from its ^{1}H NMR spectra acquired in the presence of (+)-Eu(tfc)$_3$, a chiral shift reagent

(6) (a) Carr, J. A.; Al-Azemi, T. F.; Long, T. E.; Shim, J. Y.; Coates, C. M.; Turos, E.; Bisht, K. S. *Tetrahedron* **2003**, *59*, 9147. (b) Al-Azemi, T. F.; Kondaveti, L; Bisht, K. S. *Macromolecules* **2002**, *35*, 3380. (c) Kondaveti, L; Al-Azemi, T. F.; Bisht, K. S. *Tetrahedron: Asymmetry* **2002**, *13*, 129.

(7) (a) Carr, J. A.; Bisht, K. S. *Tetrahedron* **2003**, *59*, 7713. (b) Xu, C; Yuan, C. *Tetrahedron* **2004**, *60*, 3883. (c) Sundby, E.; Perk, L.; Anthonsen, T; Aasen, A. J.; Hansen, T. V. *Tetrahedron* **2004**, *60*, 521.

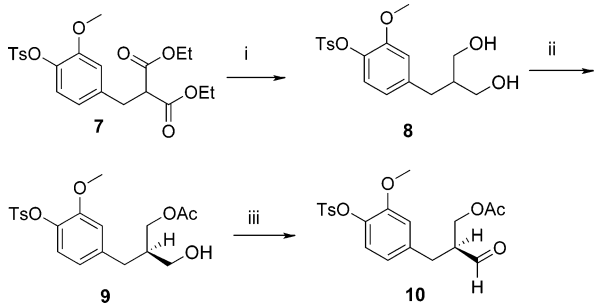
(8) Other protecting groups such as TBDMS, Bn, and PMB were initially utilized, but they proved to be liabilities during the course of the subsequent reactions, often resulting in low-yielding or failed reactions.

(9) Oeveren, A. V.; Jansen, J. F. G. A.; Feringa, B. L. *J. Org. Chem.* **1994**, *59*, 5999.

(10) Yang, C.; Pittman, C. U. *Synth. Commun.* **1998**, *28* (11), 2027.

(11) Maximum yield upon enzymatic acetylation was 62%. The unreacted diol was recovered, and acetylation was repeated with recovered enzyme to give a total yield of 90% of combined enantiopure monoacetate (**9**), $[\alpha]^{25}_D$ = +7.9°.

Scheme 3[a]



[a] Conditions: (i) $NaBH_4$, LiCl in MeOH/ether (1:3), 0 °C, 24 h, 89%; (ii) vinyl acetate, PS-30, 40 °C, 48 h, 90%; (iii) Dess−Martin periodinane, CH_2Cl_2, rt, 6 h, 75%.

(Figure 1). The resonance signal of the methoxy and acetoxy protons in the racemic mixture, singlets in absence of the chiral shift reagent, was split into a set of two signals of equal intensity for the two enantiomers in the presence of

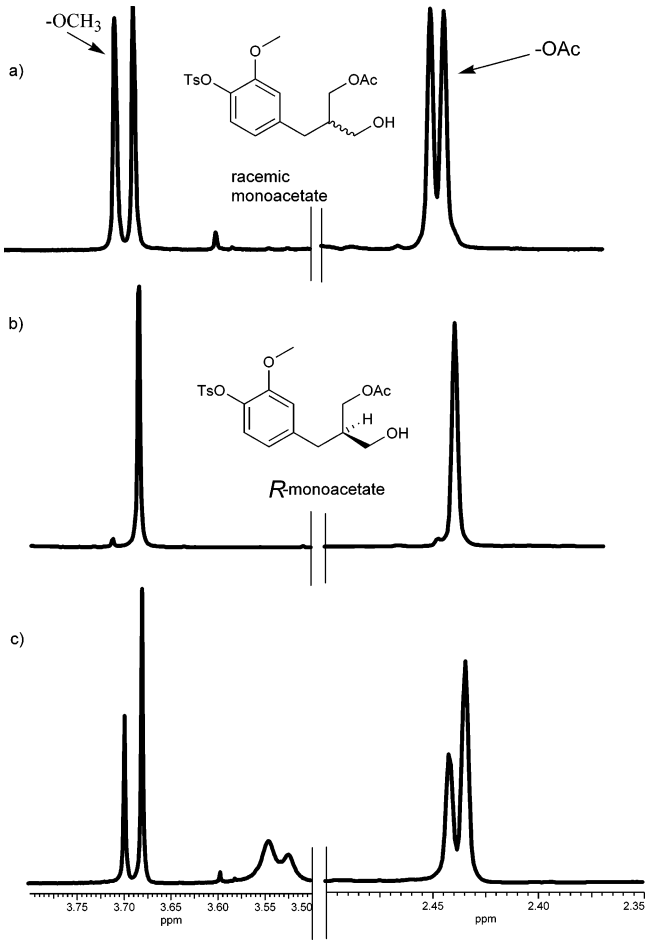


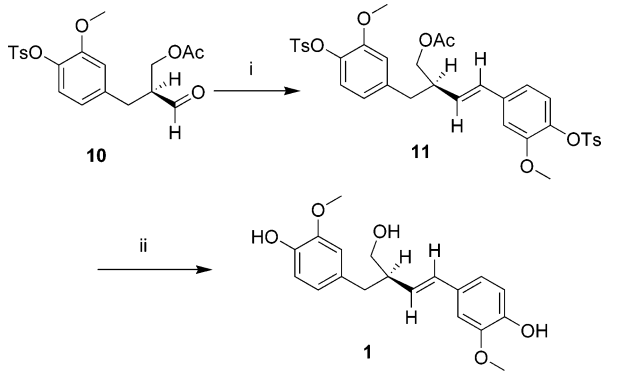
Figure 1. (a) ^{1}H NMR of racemic monoacetate (**9**) with (+)-Eu(tfc)$_3$. (b) ^{1}H NMR of enantiorich monoacetate by PS-30 with (+)-Eu(tfc)$_3$. 9c) ^{1}H NMR of racemic and enantiorich monoacetate with (+)-Eu(tfc)$_3$. All spectra were taken in $CDCl_3$ at 25 °C at 500 MHz.

(+)-Eu(tfc)$_3$.[12] The product monoacetate (**9**) obtained by lipase desymmetrization reveals a singlet for both the methoxy and acetoxy protons in the presence of (+)-Eu(tfc)$_3$.[12]

The enantiomerically enriched monoacetate was oxidized to the aldehyde (**10**), which was particularly sensitive to the choice of oxidizing agent used. Oxidation with pyridinium chlorochromate (PCC) or with Parikh−Doering reagent (SO_3·pyridine) failed to furnish the desired aldehyde **10**. Instead, an appropriately substituted 2-benzylacrolein was isolated, which we believe results upon β-elimination of the acetoxy group in **10** with loss of acetic acid. However, Dess−Martin periodinane in dry dichloromethane at 0 °C gave the desired product **10** in 75% yield with minimal side reaction. It is important to note that when the reaction was allowed to proceed for longer than 6 h, the yield of the undesired β-elimination side product leading to the loss of acetic acid increased substantially. Because of its instability, the aldehyde **10** was taken directly to the next step without further purification.

The final assembly of (*R*)-(−)-imperanene began with the coupling of aldehyde **10** with Wittig reagent **6** that was synthesized in Scheme 1. The *trans*-pertosylated imperanene (**11**) was the favored diastereomer of the product alkene (88%, a 9:1 diastereomeric ratio) (Scheme 4).[13] The isomers

Scheme 4[a]



[a] Conditions: (i) **6**, *n*-butyllithium, 0 °C, 24 h, 88%; (ii) KOH, ethanol, reflux, 3 h, 60%.

were separated by wet column chromatography over silica gel. Global deprotection of the *p*-tosyl and acetyl protecting groups was achieved by refluxing isomer **11** in ethanolic KOH for 3 h followed by chromatographic purification to yield (*R*)-(−)-imperanene in 60% yield. The specific rotation value of the product matched with that of the (*R*)-(−)-imperanene reported in the literature ($[\alpha]^{25}_D = -98.2°$ (*c* 0.011 g/mL, $CHCl_3$)).[14]

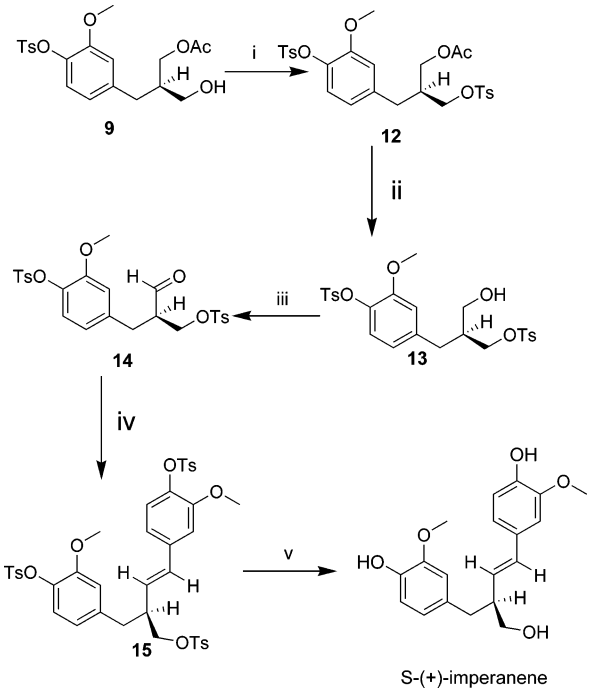
To synthesize the (*S*)-(+)-imperanene, inversion of stereochemistry in the monoacetate was accomplished after the

(12) The enantiomeric excess was determined from the ^{1}H NMR spectrum recorded in the presence of the (+)-Eu(tfc)$_3$ using the following equation: ee = [(*R*) − (*S*)]/[(*R*) + (*S*)] × 100%.

(13) The diastereomeric ratio was determined via ^{1}H NMR by comparing the ratio of the alkenyl protons of the crude reaction mixture.

enantiopure monoacetate (**9**) was tosylated with tosyl chloride in dichloromethane using triethylamine/DMAP to furnish **12** (yield = 93%) (Scheme 5). Deacetylation of **12** using K_2CO_3 in methanol gave the mono-ol (**13**) in 86% yield, which was oxidized under conditions previously stated to give the desired aldehyde **14**. The aldehyde (**14**) proved to be more stable than its acetylated counterpart (**10**). This stability is probably due to a steric encumbrance of the β-tosyl group, suppressing elimination of the α-proton. Similarly, the final assembly of (*S*)-(+)-imperanene began with the coupling of aldehyde **14** with the Wittig reagent **6** to give **15** (yield = 72%), in a diastereomeric ratio 7:1 in favor of the *trans*-stereoisomer. Separation of diastereomers was accomplished via wet column chromatography, and removal of the *p*-tosyl protecting groups in refluxing ethanolic KOH gave (*S*)-(+)-imperanene in 56% yield ($[\alpha]^{25}_D = +104°$ (*c* 0.01 g/mL, $CHCl_3$)).[14]

Scheme 5[a]



[a] Conditions: (i) tosyl chloride, triethylamine, DMAP, dry CH_2Cl_2, 0 °C, 93%; (ii) K_2CO_3, MeOH, 0 °C, 87%; (iii) Dess−Martin periodane, CH_2Cl_2, rt, 6h, 83%; (iv) **6**, *n*-butyllithium, THF, 0 °C, 80%; (v) KOH, ethanol, reflux, 3 h, 56%.

In conclusion, an enantioselective synthesis of both (*S*)-(+)- and (*R*)-(−)-imperanene has been demonstrated starting from vanillin, with overall yields of 19% and 24%, respectively. In the core reaction, PS-30 served as the biocatalyst for asymmetrization of the prochiral diol (**8**), providing the monoacetate (**9**) in enantiomeric excesses of >97%. The specific rotation values are in agreement with reported literature values.

Acknowledgment. Financial support for this work from the American Cancer Society, the Herman Frasch Foundation, and the American Lung Association is greatly appreciated.

Supporting Information Available: Complete experimental procedure and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048802C

(14) Although the natural imperanene was reported to have $[\alpha]^{25}_D = +700$ by Matsunaga et al.[1], Doyle et al.[2] reported $[\alpha]^{25}_D = +103$ for 93% enantioenriched sample and have explained the discrepancy in reported $[\alpha]^{25}_D$ for natural product and observed value for the synthetic sample.