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Enantioselective Synthesis of Imperanene, a Platelet Aggregation Inhibitor

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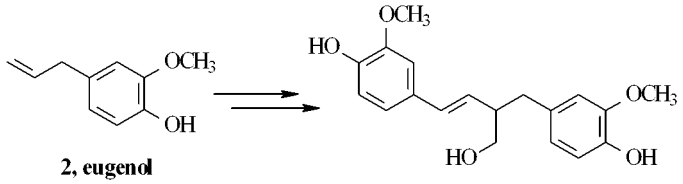
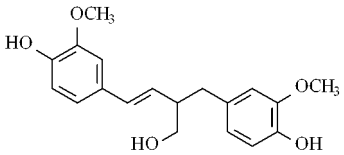
ABSTRACT



2, eugenol **1, imperanene**

Both enantiomers of imperanene, a platelet aggregation inhibitor, have been synthesized in 82–90% ee. The key step of establishing the chiral center was achieved through stereoselective alkylation with benzyl chloromethyl ether using Enders' *R*AMP/SAMP chiral auxiliary method. The natural product was determined to be the (*S*)-enantiomer through comparison of optical rotation data.

Imperanene (**1**) is a phenolic compound isolated from the rhizomes of the plant *Imperata cylindrica*.[1] This plant is used in Chinese traditional medicine as an antiinflammatory and diuretic agent. Imperanene was found to completely inhibit rabbit platelet aggregation induced by thrombin at a concentration of 6×10^{-4}M.



1 Imperanene

Other members of this rare C_6-C_4-C_6 class of natural products have also shown biological activity,[2] including antiplatelet aggregation.[3] The search for new platelet aggregation inhibitors to treat diseases such as heart attack and stroke is a very active research area. While imperanene was isolated as a single enantiomer, the configuration of the stereogenic carbon was not determined. The mode of action of imperanene remains unexplored. The synthesis of both enantiomers of imperanene is an important first step in further studies on this class of compounds. We have synthesized both enantiomers of imperanene in an eight-step synthesis with 82−90% ee.

The key step of asymmetric induction utilizes Enders' method with the chiral auxiliary (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) or the (*R*)-enantiomer (*R*AMP).[4] The chiral auxiliary reacts with an aldehyde to form a hydrazone that can then be alkylated. The enantiofacial selectivity of alkylation is dependent on whether *R*AMP or *S*AMP is used. This versatile route allows for formation of both enantiomers of imperanene through a parallel reaction sequence.

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(2) (a) Ishida, M.; Hamasaki, T.; Hatsuda, Y. *Agric. Biol. Chem.* **1975**, *11*, 2181. (b) Green, D.; Kashman, Y.; Miroz, A. *J. Nat. Prod.* **1993**, *56*, 1201.

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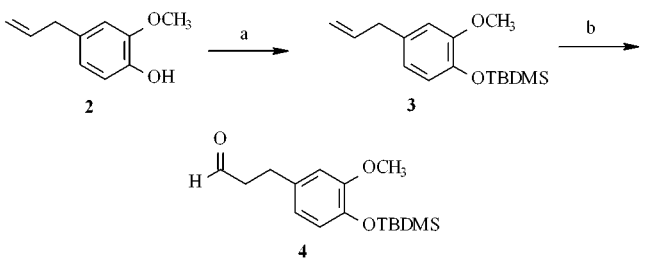
Our synthesis of imperanene begins with the formation of the appropriate aldehyde for the Enders' sequence (Scheme 1). Protection of eugenol (**2**) gave silyl ether **3** in

Scheme 1[a]

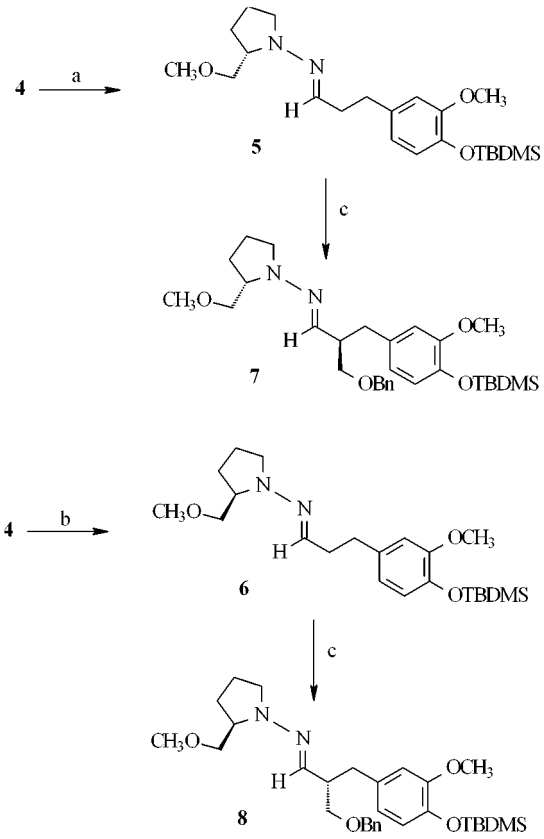


[a] (a) *tert*-Butyldimethylsilyl chloride, imidazole, DMF, rt, 19 h, 78%; (b) (i) disiamylborane, 0 °C, 3 h; (ii) PCC, CH_2Cl_2, reflux, 2 h, 75%.

78% yield. Following a procedure of Brown and co-workers,[5] treatment of **3** with disiamylborane and subsequent oxidation with pyridinium chlorochromate afforded aldehyde **4** in 75% yield.

The asymmetric alkylation steps (Scheme 2) involve the reaction of **4** with the *S*AMP chiral auxiliary to generate

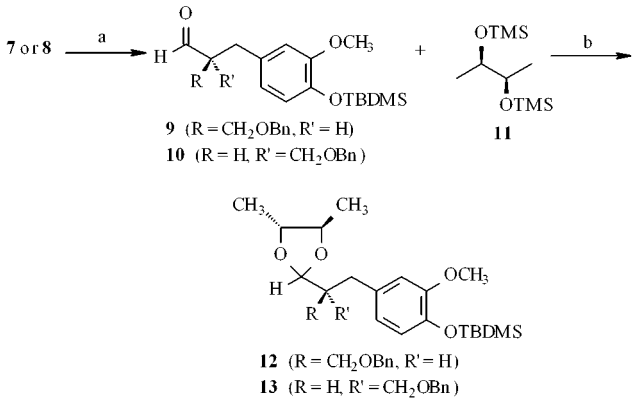
Scheme 2[a]



[a] (a) *S*AMP, 0 °C → rt, 20 h, 84%; (b) *R*AMP, 0 °C → rt, 20 h, 82%; (c) (i) LDA, 0 °C, 5.5 h; (ii) benzyl chloromethyl ether, −120 °C for 20 min, then rt for 20 h, (77% for **7**, 75% for **8**).

chiral hydrazone **5** in 84% yield. In a separate reaction, **4** was converted to the *R*AMP-based hydrazone **6** in 82% yield. Benzyl chloromethyl ether[6] was used as the alkylating agent in the Enders' reaction sequence to introduce a one-carbon benzyl-protected alcohol group in a single step. Deprotonation of **5** with LDA and alkylation with benzyl chloromethyl ether at −120 °C gave a 77% yield of the (*R*)-enantiomer **7**. The corresponding (*S*)-enantiomer **8** was formed in 75% yield from **6**. Determining the diastereomeric excess for the alkylated hydrazones was problematic. Analysis of ^1H and ^{13}C NMR spectra and the use of NMR chiral shift reagents were unsuccessful. The stereoselectivity of the alkylation reaction was determined after removal of the *R*AMP/*S*AMP chiral auxiliary as shown in Scheme 3.

Scheme 3[a]



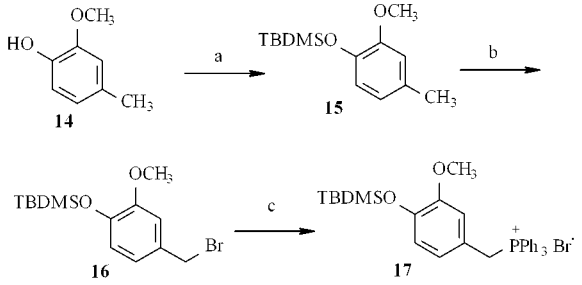
[a] (a) Ozone, CH_2Cl_2, −78 °C, 30 min, (79% for **9**, 75%for **10**); (b) TMSOTf (cat.), CH_2Cl_2, −78 °C for 3 h, then 0 °C for 1 h, (76% for **12**, 72% for **13**).

Ozonolysis of the alkylated hydrazones **7** and **8** at −78 °C removed the chiral auxiliary to form aldehydes **9** and **10**, respectively. For determining the enantioselectivity of the alkylation step, aldehydes **9** and **10** were combined with the (*R*,*R*)-diol derivative **11** to give acetals **12** and **13**, respectively.[7] The ^{13}C NMR spectra of these acetals were analyzed to determine the ee values. The chiral shift reagent $Eu(fod)_3$ enhanced the separation of the carbon signals to improve the resolution. The alkylation reaction was highly selective with an enantiomeric excess of 82−90% for **12**, the acetal of aldehyde **9** formed from the *S*AMP reaction sequence. The ee of **13**, the acetal of aldehyde **10** formed from the *R*AMP reaction sequence, ranged from 82 to 89%.

The final assembly of imperanene involved the coupling of aldehyde **9** or **10** with the Wittig reagent synthesized as shown in Scheme 4. Protection of 2-methoxy-4-methylphenol **14** gave **15** in 86% yield, which upon benzylic bromination,

(5) Brown, H. C.; Kulkarni, S. U.; Rao, C. G. *Synthesis* **1980**, 151.
(6) Connor, S. J.; Klein, G. W.; Taylor, G. N.; Boeckman, R. K.; Medwid, J. B. In *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 101.
(7) (a) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, *18*, 2183. (b) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357. (c) Parker, D. *Chem. Rev.* **1991**, *91*, 1441.

Scheme 4[a]

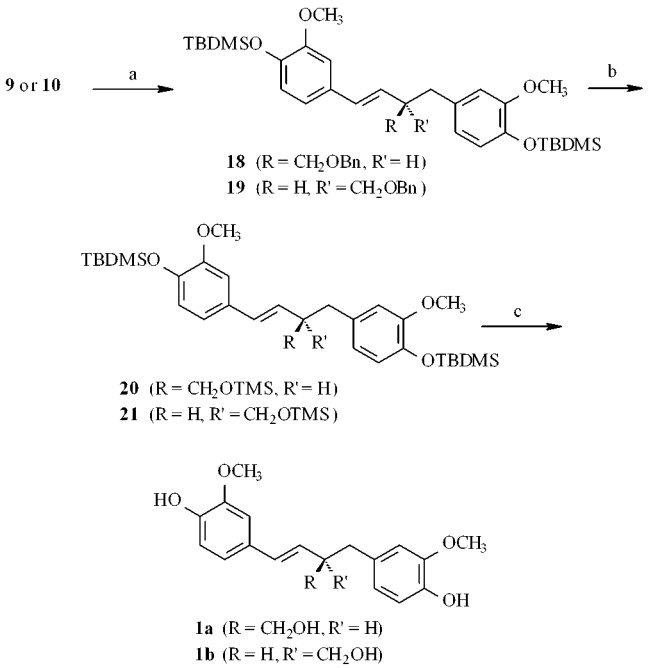


[a] (a) TBDMSCl, imidazole, DMF, rt, 3 h, 86%; (b) NBS, benzoyl peroxide (cat.), CCl_4, reflux, 3 h; (c) PPh_3, toluene, reflux, 19 h, 50% from **15**.

afforded the alkyl bromide **16**, following the literature procedure.[8] This compound was unstable and therefore was used in the next step directly without purification. Treatment of **16** with triphenylphosphine gave the desired Wittig reagent **17** in 50% yield from **15**.

Aldehyde **9** was coupled to **17** to produce alkene **18** in a 5:1 ratio of the desired *trans* alkene to the *cis* isomer. (Scheme 5) Purification by silica gel flash chromatography

Scheme 5[a]



[a] (a) *n*-BuLi (2 equiv), **17** (2 equiv), THF, 0 °C (30 min) → rt (19 h), **18** = 72%, **19** = 63%; (b) $PhSSiMe_3$(10 equiv), *n*-Bu_4NI (1.5 equiv), ZnI_2 (5 equiv), $ClCH_2CH_2Cl$, rt, **20** = 65%, **21** = 59%; (c) TBAF (3.3 equiv), THF, rt, 30 min, **1a** = 82%, **1b** = 75%.

successfully removed the minor *cis*-isomer. In optimizing the Wittig reaction, the choice of base and the reaction temperature were manipulated to improve both the yield and the *trans*-selectivity. The use of NaHMDS, KHMDS, and potassium *tert*-butoxide as bases led to elimination of the benzyl group from **9**. Using the cosolvent HMPA gave similar results. *n*-Butyllithium showed no such elimination and gave complete conversion to the desired alkene **18**. Addition of the aldehyde to the Wittig reagent at 0 °C with subsequent warming to room temperature gave the optimal *trans/cis* ratio. This same reaction with the enantiomeric aldehyde **10** produced alkene **19** in 63% yield.

Removal of the benzyl protecting group proved to be problematic. Hydrogenation, treatment with acetic or hydrochloric acid,[9] oxidation with DDQ,[10] and reaction with trimethylsilyl iodide[11] were all either low-yielding or unsuccessful. Our initial effort at debenzylation through the use of phenylthiotrimethylsilane, zinc iodide, and tetrabutylammonium iodide at reflux for 2 h, following the literature conditions,[12] led to decomposition. However, we found that in 2.5 h at room temperature, the benzyl group of **18** was converted to the trimethylsilyl group to give **20** in 65% yield. Benzyl ether **19** was converted to **21** (59% yield) in 1 h. Final removal of the silyl protecting groups by treatment with TBAF gave both enantiomers of imperanene **1a** (82%) and **1b** (75%). The synthetic imperanene showed spectroscopic properties identical to those of the natural product, and enantiomer **1b** showed a comparable optical rotation.[1] Therefore, (*S*)-imperanene is the natural and biologically active enantiomer.

In conclusion, both enantiomers of imperanene were synthesized in eight steps using the *R*AMP/*S*AMP chiral auxiliary method for asymmetric induction. Enantiomeric excess values of 82−90% have been obtained. Comparison of the optical rotation values of **1a** and **1b** to the literature value of the isolated imperanene reveals that the natural product is the (*S*)-enantiomer. This synthetic route will enable further investigation into the physiological properties of related compounds.

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

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