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Catalytic asymmetric total synthesis of (*S*)-(−)-zearalenone, a novel lipoxygenase inhibitor

Marc P. Baggelaar [a], Yange Huang [a], Ben L. Feringa [a,*], Frank J. Dekker [b], Adriaan J. Minnaard [a,*]

[a] Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands
[b] Groningen Research Institute of Pharmacy, Anthonius Deusinglaan 1, 9713 AV Groningen, The Netherlands

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ABSTRACT

A catalytic asymmetric synthesis of (*S*)-(−)-zearalenone is reported using asymmetric allylic alkylation for the introduction of the stereocenter. (*S*)-(−)-Zearalenone turned out to be a novel lipoxygenase inhibitor.

Resorcylic acid lactones are mycotoxins produced by various strains of fungi via polyketide biosynthesis. These medium-sized macrocyclic lactones exhibit a wide variety of interesting biological activities,[1] among which selective kinase inhibition has been characterized very well.[2] Zearalenone, probably the best known member of the resorcylic acid lactones, was first isolated from *Gibberella zeae* in 1962[3] and four years later its structure was elucidated.[4] Zearalenone shows estrogen agonistic properties most likely because its macrocycle can adopt a confirmation that is similar to steroids.[1e] Also of interest, is the fact that related 6-alkylsalicylates inhibit histone acetyl transferase activity.[5] In addition, Zearalenone has been shown to exhibit antibacterial, uterotropic and anabolic activity.[3,6] We envisioned that the salicylate core structure in Zearalenone could provide lipoxygenase inhibitory activity for this compound,[7] which has been indeed observed in this study.

Many of the synthetic routes to Zearalenone **1** either lead to the racemate,[8] are based on natural chiral starting materials,[9] or on chiral auxiliaries.[10] Some groups used kinetic resolution or an enzymatic approach to obtain the chiral building blocks.[11] We felt that a more concise synthesis of Zearalenone **1** that takes advantage of a highly efficient and enantioselective catalytic allylic alkylation would make this compound more readily available for biological studies. Herein, we report the asymmetric synthesis of **1** in an efficient and selective manner and describe its utilization for the inhibition of lipoxygenase.

The target molecule **1** was retrosynthetically analyzed as shown in Scheme 1. We opted for a late stage double demethylation of dimethoxyzearalenone **2** to give **1**, as the dihydroxybenzene unit is too sensitive to carry through the synthesis. The 14-membered macrocycle should be installed by intra-molecular ring closing metathesis of diene **3**, and retrosynthetic cleavage of the ester moiety leads to the required acid fluoride **4** and chiral alcohol **5**. The latter one can in turn be prepared from ester **6**, provided by enantioselective copper-catalyzed asymmetric allylic alkylation developed in our group.[12]

The synthesis started from commercially available **7** as described in Scheme 2. Vilsmeier–Haack formylation[13] of **7** afforded the aldehyde **8** in 82% yield, followed by Stille cross coupling with tributylvinyltin[14] to give compound **9** in 84% yield. Pinnick oxidation of aldehyde **9** gave acid **10** in 85% yield.[13] Carboxylic acid **10** was subsequently transformed into the corresponding acid fluoride using cyanuric fluoride.[15]

The synthesis of chiral alcohol **5** started from readily available **11** using a copper/TaniaPhos catalyzed asymmetric allylic alkylation with methylmagnesium bromide which afforded ester **6** in high yield and excellent enantioselectivity (82% and 98%, respectively, Scheme 3).[12] Hydrolysis of the ester **6** by aqueous KOH, followed by protection of the resulting alcohol using *tert*-butyldiphenylsilyl chloride (TBDPSCl), gave alkene **12** in an overall yield of 80%. Initial hydroboration of the terminal alkene using borane, after oxidation, afforded the alcohol as a mixture of regioisomers. However, 9-borabicyclononane (9-BBN) provided, after oxidation, primary alcohol **13** selectively. Alcohol **13** was sub-

* Corresponding authors.
E-mail address: A.J.Minnaard@rug.nl (A.J. Minnaard).

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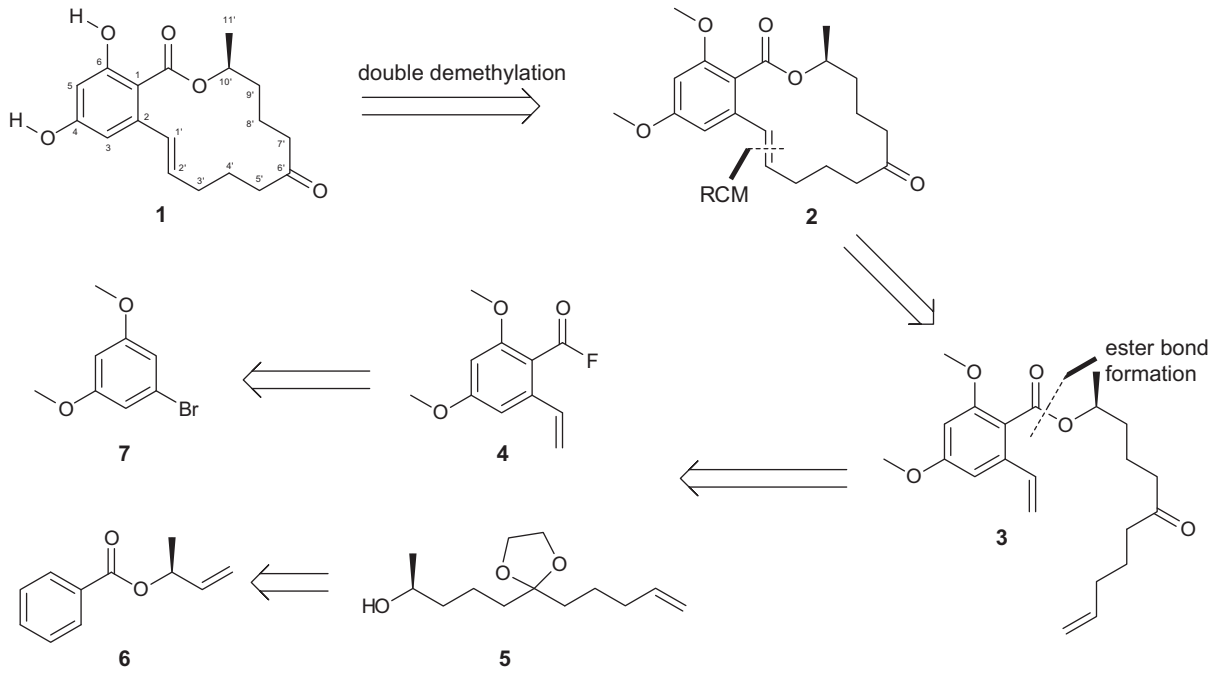
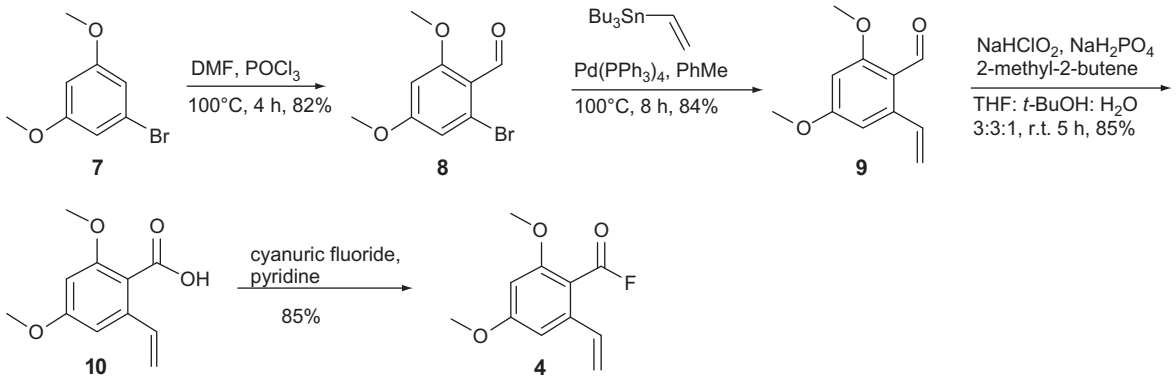


Scheme 1. Retrosynthetic analysis of Zearalenone.



Scheme 2. Synthesis of the building block **4**.

sequently transformed into iodide **14** using iodine and triphenylphosphine in high yield.

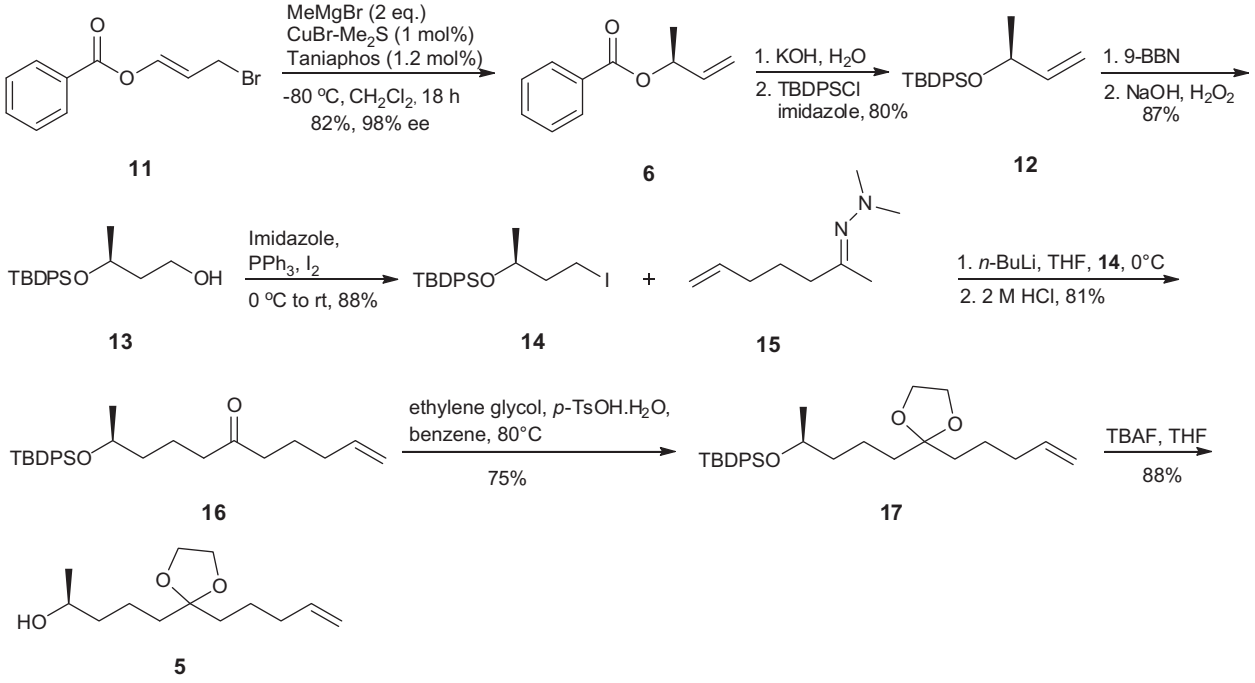
The synthesis of coupling partner hydrazone **15** (Scheme 4) started from a copper catalyzed addition of pentenylmagnesium bromide to acetyl chloride **18** to provide ketone **19** in 75% yield.[16] Hydrazone formation from **19** using dimethyl hydrazine in acetic acid and ethanol resulted in 88% yield.[17]

Initial synthesis of ketone **16** by coupling of the corresponding tosylate of **13** with **15** resulted in complicated products. However, the α-alkylation of **15** with iodide **14**, when carried out via the lithiated dimethylhydrazone, gave the desired product in high yield and complete regioselectivity.[18] Ketone **16** was subsequently obtained by in situ hydrolysis. Before removal of the TBDPS group the ketone had to be protected, as without this modification the compound would suffer loss of enantiopurity by a reversible intramolecular hydride shift as already reported in 1968 by Wendler and co-workers[8a] Acetal protection of the ketone using ethylene glycol with a catalytic amount of *p*-TsOH in benzene gave **17** in 75% yield. Finally, removal of the silyl group by tetrabutylammonium fluoride (TBAF) in THF gave the desired building block **5** in 88% yield.

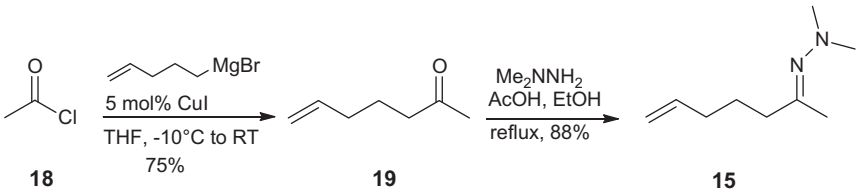
Esterification of alcohol **5** and carboxylic acid **10** using carbodiimide-based coupling reagents or the Yamaguchi reagent did not provide any desired product. This was anticipated as the acid function in **10** is sterically severely hindered. Fortunately, Fürstner et al. solved this problem by using fluoride as the 'smallest possible' leaving group.[19] Acid fluoride **4** can be easily prepared from the corresponding acids with cyanuric fluoride. Coupling with alcohol **5** gave the desired product **20** in high yield (Scheme 5).

Ring closing metathesis of **20** using the Grubbs second generation catalyst gave the desired *E*-alkene **21** in high yield.[10b] Subsequent hydrolysis of the acetal under aqueous acidic conditions went smoothly and gave (*S*)-(−)-zearalenone dimethyl ether in 83% yield.

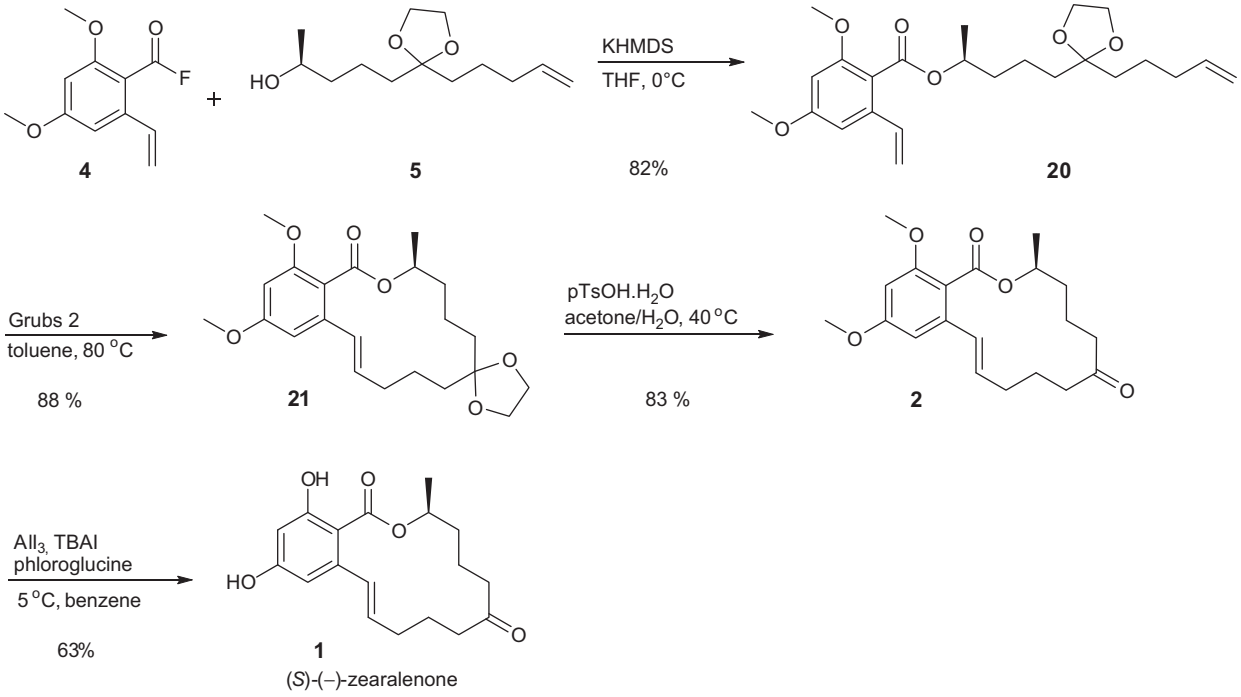
Demethylation of **2** and related compounds is a recognized problem as it requires harsh conditions. Initial attempt using AlI_3 with tetrabutylammonium iodide reported by Yadav and Murthy[11e] led to complex mixtures. Fortunately, the improved method reported by Maier and co-workers[20] using phloroglucine as an iodine scavenger works very well. The final product, (*S*)-(−)-zearalenone **1**, was obtained in 63% yield and spectroscopic data were in agreement with the reported data.[11d]



Scheme 3. Synthesis of chiral alcohol **5**.



Scheme 4. Synthesis of hydrazone **15**.



Scheme 5. Assembly of the building blocks to provide (*S*)-(−)-zearalenone.

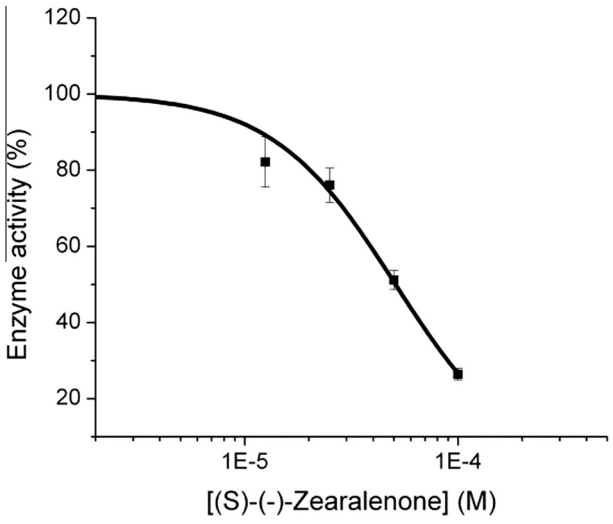


Figure 1. Concentration dependent inhibition of soybean lipoxygenase-1 (SLO-1) by (*S*)-(−)-zearalenone.

Lipoxygenase inhibition by (*S*)-(−)-zearalenone was investigated using a spectrophotometric assay for the conversion of linoleic acid into hydroperoxy eicosatetraenoic acid (HPETE). Enzyme inhibition was measured by the residual enzyme activity after 10 min incubation with the inhibitor at room temperature. The product formation was followed by UV absorbance of the conjugated diene at 234 nm ($\varepsilon = 25{,}000\ M^{-1}\ cm^{-1}$) over a period of 20 min and started 10 s after the addition of the substrate linoleic acid. The inhibitory concentration 50% (IC_{50}) was determined by measuring the enzyme activity using various concentrations of (*S*)-(−)-zearalenone (12.5, 25, 50 and 100 μM, Fig. 1). The enzyme activity without inhibitor was setto 100% and the activity in presence of various concentrations inhibitor were calculated accordingly. The average and standard deviation of three experiments were plotted.

An inhibitory concentration 50% (IC_{50}) of 51 ± 2 μM was observed for inhibition of soybean lipoxygenase-1 (SLO-1) by (*S*)-(−)-zearalenone, which indicates a modest inhibitory potency. This observation is of interest because lipoxygenase inhibition by salicylate esters has not been described previously. Thus, (*S*)-(−)-zearalenone represents a novel structural class for development of lipoxygenase inhibitors.

In conclusion, we report a novel efficient total synthesis of (*S*)-(−)-zearalenone that involves a highly enantioselective catalytic asymmetric allylic alkylation as a key step. Interestingly, this compound demonstrates a modest inhibitory activity of lipoxygenase activity, which demonstrated that the resorcyclic acid lactones could provide valuable starting points for development of lipoxygenase inhibitors of a novel structural class. The reported synthetic route enables elucidation of structure–activity relationships for this compound class in future studies.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.06.024.

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