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Graphical Abstract

Stereoselective total synthesis of (–)-zeylenol, a key intermediate for the synthesis of (+)-pipoxide, (–)-uvarigranol G and (–)-tonkinenin A

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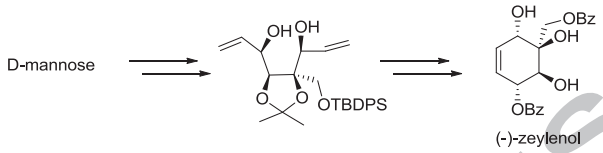
Allam Vinaykumar[a], Chinthala Muniraju[a] and Batchu Venkateswara Rao*[a]



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Stereoselective total synthesis of (–)-zeylenol, a key intermediate for the synthesis of (+)-pipoxide, (–)-uvarigranol G and (–)-tonkinenin A

Allam Vinaykumar[a], Chinthala Muniraju[a] and Batchu Venkateswara Rao*[a]

[a] *Organic & Biomolecular Chemistry Division, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad-500 007, India.*

* Corresponding author. Tel./ fax: +91 40 27193003; *E-mail addresses*: venky@iict.res.in , drb.venky@gmail.com.

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ABSTRACT

Total synthesis of (–)-zeylenol, a key intermediate for the synthesis of (+)-pipoxide, (–)-uvarigranol G and (–)-tonkinenin A was achieved from commercially available starting material D-mannose. The key steps are mixed aldol condensation, Grignard reaction, ring closing metathesis and regioselective benzoylation.

Introduction

Polyoxygenated cyclohexene unit having benzoyloxy methyl or hydroxyl methyl functionalities on a tertiary carbon is a popular moiety present in many natural products. The first example of this category is (–)-zeylenol **1**. Interestingly zeylenol exists in nature in both enantiomeric forms and both have shown important biological activity. (–)-Zeylenol **1** was isolated by Cole and Bates[1] in 1981 from the plant *uvaria zeylanica*. The absolute configuration of (–)-zeylenol was then confirmed by Ganem using chemical correlation and circular dichroism spectroscopy.[2] Also there are some reports which describe the isolation of (–)-zeylenol without determining the absolute configuration.[3,4] Later, the enantiomer (+)-zeylenol was also isolated from a natural source *kaempferia* species[6] and also from *uvaria*[7] and piper.[8] (+)-Zeylenol shows selective cytotoxicity towards HL-60 leukemia cells.[6c] (–)-Zeylenol **1** shows antitumor, antifeedant activity[12] and also anti-inflammatory activity. Moreover, (–)-zeylenol exhibits moderate cytotoxic activity in human breast cancer cell lines MDA-MB231 (IC_{50} 54.22 μM) with SD ±10.20 but with a lesser extent in hepatocellular carcinoma HepG2.[15] Numerous natural products which are having zeylenol skeleton have been isolated from different sources and are showing interest biological activity.[5-14] (–)-Uvarigranol G **2**, (–)-tonkinenin A **3,** (+)-pipoxide **4**, ferrudiol **5** and uvaribonol A **6** (Figure 1) are some examples belong to this class whose absolute configuration have been established.[5–14]

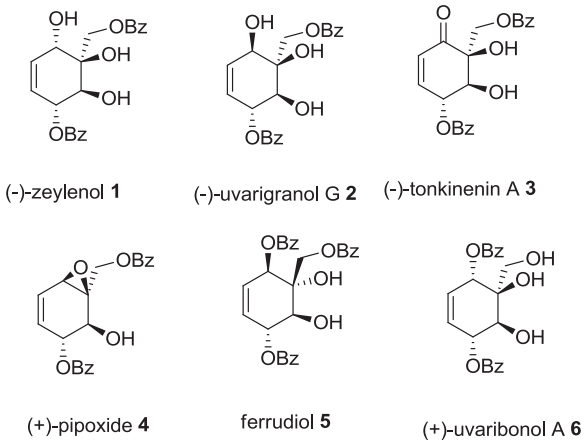
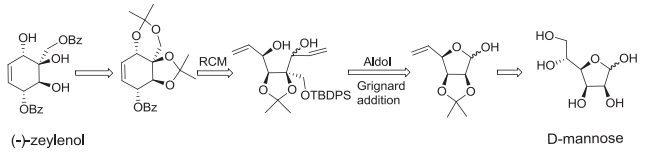


Figure 1. Some natural products in the zeylenol family.

So far only Ogasawara *et al*. has reported both formal[16a] and total[16b,c] enantiocontrolled synthesis of (–)-zeylenol **1** which has been utilized for the synthesis of (–)-uvarigranol G **2**, (–)-tonkinenin A **3** and (+)-pipoxide **4**. The key material for their synthesis is the chiral cyclohexenoid building block which was prepared from *meso* ene diol. Palframan *et al*[17] synthesized (+)-zeylenol and zeylenones from *ipso, ortho* diols using

photooxygenation of a microbial arene and regioselective Kornblum–DeLaMare Rearrangement. To the best of our knowledge, nobody has synthesized these molecules from chiral starting materials. For the past few years, we have been carrying out the research in the synthesis of polyhydroxy cyclohexene compounds which are commonly known as carbasugar by using ring closing metathesis approach.[18] Herein we report a stereoselective approach to (–)-zeylenol starting from D-mannose.

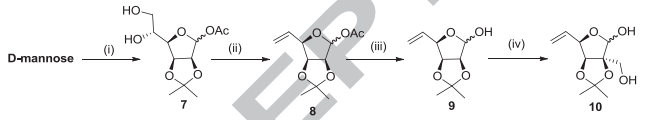
In the present approach we have used mixed aldol condensation[19], Grignard reaction, ring closing metathesis[20] and regioselective benzoylation[21] reactions as key steps for a short synthesis of (–)-zeylenol in good overall yield.



Scheme 1: Retrosynthetic Analysis

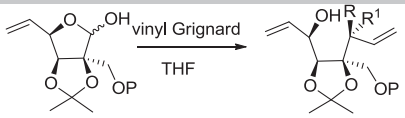
Results and Discussion:

Based on the retrosynthetic analysis (Scheme 1) we have chosen D-mannose as a starting material which is a cheap and commercially available. D-Mannose was converted to diol **7** in 97% yield by reported method.[22] Application of Garregg's protocol[23] on diol **7** yielded olefin compound **8**[24]. Deprotection of acetate in **8** gave free lactol **9**[24]. Next step is the introduction of hydroxymethyl group selectively at C-2. For this, Compound **9** was subjected to the mixed aldol reaction[19] with formaldehyde in presence of K_2CO_3 to yield **10**[25]. (Scheme 2).



Scheme 2: *Reagents and conditions*: (i) see ref.[22]; (ii) imidazole, TPP, I_2, DCM, rt (80%); (iii) K_2CO_3, MeOH, rt (90%); (iv) K_2CO_3, 37% aq.HCHO, MeOH, 80°C (90%).

To make diene precursor for RCM, we tried vinyl Grignard addition on compound **10** which failed to give the desired product and every time the starting material was recovered. The inertness of substrate **10** towards Grignard addition even with excess reagent might be due to the presence of free hydroxyl group adjacent to the lactol. To circumvent this, we protected the primary alcoholic group in **10** as TBDPS ether to get **11**[25] by treating with TBDPS-Cl, imidazole and DMAP (cat.). Vinyl Grignard addition on **11** afforded two diastereomers *syn* **12** and *anti* **13** in 1:3 ratio which were separated by column chromatography.



10 P=H
11 P= TBDPS

12 R=H,R'=OH
13 R=OH,R'=H

Table 1: Vinyl Grignard addition on compounds **10** and **11**:

Entry	Conditions (equivalents)	Temperature (°C)	Time (h)	Yield (%)
10	4	–78°C -r.t.	12	N.R
10	4	0°C -r.t.	12	N.R
11	4	–78°C -r.t.	12	75% (*dr* : 1:3)[a]

NR = no reaction; [a] = *dr* ratio is shown as *syn:anti* and confirmed by ^{1}H NMR

The formation of major diastereomer **13** can be explained *via* chelation controlled transition states **A** or **B** (Figure 2). In the seven membered transition state[26] **A**, the TBDPS ether group blocks one of the faces, so the nucleophile will attack from the opposite face to give the major isomer **13** or addition may be taking place *via* transition state **B**.

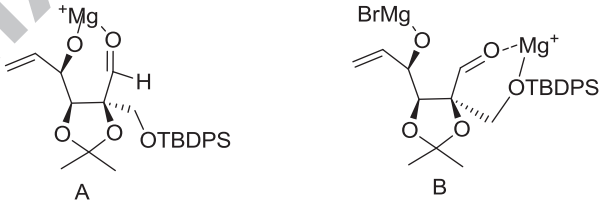
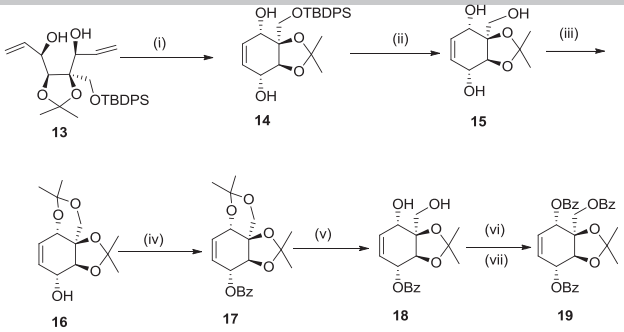


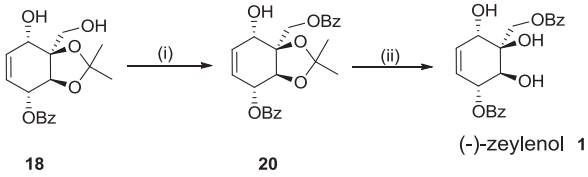
Figure 2: Chelation controlled transition state.

Ring closing metathesis reaction was carried out on **13** using Grubbs II generation catalyst[27] to give substituted cyclohexene **14**. Cleavage of TBDPS ether in **14** with TBAF resulted in the formation of 1, 3 diol **15**. To achieve the selective benzoylation in **15** it is required to mask primary and one of the allylic hydroxyl groups in compound **15**. For this, compound **15** was treated with 2, 2-DMP and *p*-TSA (cat.) to give acetal **16**. The allylic hydroxyl group in **16** was converted to benzoyl ester **17** with triethylamine, benzoyl chloride and DMAP(cat.). Selective acetonide deprotection in **17** was achieved with 80% *aq*.AcOH to furnish the diol **18**. To complete the synthesis of (–)-zeylenol, selective benzoylation of primary hydroxyl group has to be carried out. For this conversion, bases like triethylamine and pyridine were tried in the presence of benzoyl chloride at various temperatures. All the time it gave only tri benzoate **19** as a sole product (Scheme 3).



Scheme 3: *Reagents and conditions*: (i) G-II catalyst, toluene, reflux (80%); (ii) TBAF, THF, rt (90%); (iii) 2,2-DMP, *p*-TSA(cat.) (80%); (iv) BzCl, Et_3N, DMAP (cat.), 0°C–rt (85%) (v) 80% *aq*. AcOH (80%). (vi) BzCl, pyridine, DMAP (cat.), 0°C–rt (75%); (vii) BzCl, Et_3N, DMAP (cat.), 0°C–rt (70%).

Finally, selective benzoylation was achieved by treating with 1 equivalent of benzoyl chloride and 3 equivalents of collidine[20] in dry DCM at –78 °C for 3 h and then at room temperature for another 1 h to get **20**. Deprotection of acetonide under acidic conditions gave target molecule (–)-zeylenol **1** in 70% yield (Scheme 4).



Scheme 4: *Reagents and conditions*: (i) BzCl, collidine, DMAP (cat.), –78°C–rt (80%); (ii) TFA, H_2O, rt (70%).

Conversion of (–)-zeylenol **1** to (–)-uvarigranol G **2**, (–)-tonkinenin A **3**, (+)-pipoxide **4** has already been reported by Ogasawara's group.[16b]

3. Conclusions :

In conclusion, we have successfully developed a strategy for the synthesis of (–)-zeylenol **1** based on mixed aldol condensation reaction, Grignard addition, ring closing metathesis and regioselective benzoylation with an overall yield of 9%. Compound **1** is also a common intermediate for making **2**, **3** & **4**.

4. Acknowledgments:

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Highlights

- An efficient stereoselective total synthesis of (–)-zeylenol.
- (–)-zeylenol is a precursor of (+)-pipoxide, (–)-uvarigranol G & (–)-tonkinenin A.
- This strategy can be used in the synthesis of many zeylenol related compounds.