

Stereoselective synthesis of (–)-microcarpalide

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Abstract—A stereoselective approach for the synthesis of the bio-active decanolactone (–)-microcarpalide was achieved from chiral pool tartaric acid. The synthesis of pivotal intermediates *en route* to the decanolactone was achieved from α -benzyloxy aldehydes derived from L- and D-tartaric acid.

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(–)-Microcarpalide (**1**), is a 10-membered lactone of polyketide origin isolated by Hemscheidt's group from the fermentation broths of an unidentified endophytic fungi.¹ Microcarpalide is similar in structure to other fungal decanolides such as herbarumin I (**2**), herbarumin II (**3**) and lethaloxin (**4**) and is found to be weakly cytotoxic to mammalian cells and acts as a microfilament disrupting agent (Fig. 1). Since the isolation of microcarpalide, a number of syntheses have appeared in the past few years.² Most of the approaches towards the synthesis of microcarpalide were centred either on ring closing metathesis (RCM) of a suitably protected diene ester of type **6** or on Yamaguchi lactonization of a suitable linear hydroxy acid as the key step.

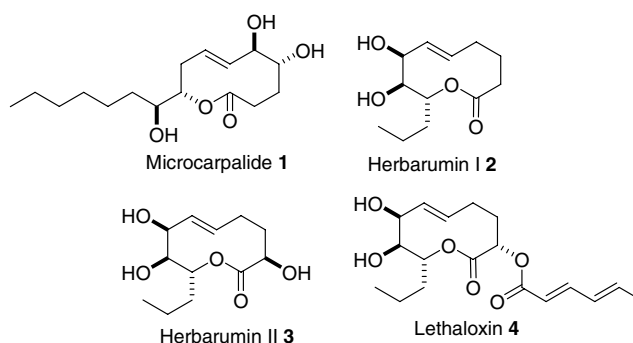
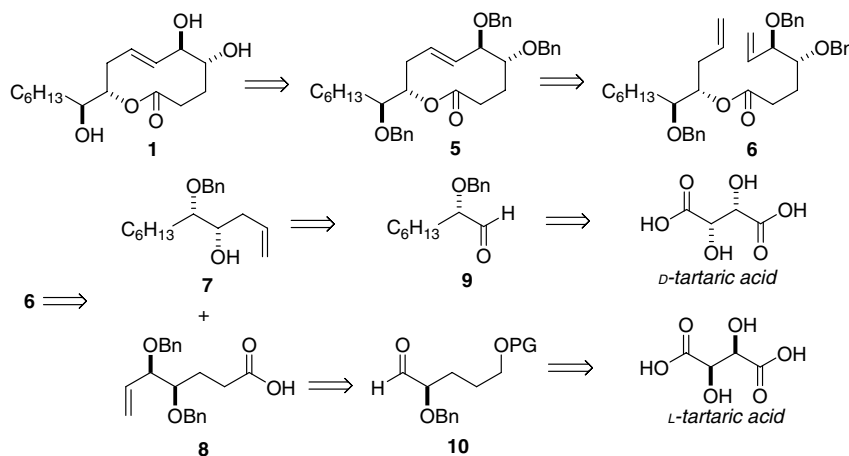


Figure 1. Bioactive fungal decanolactones.



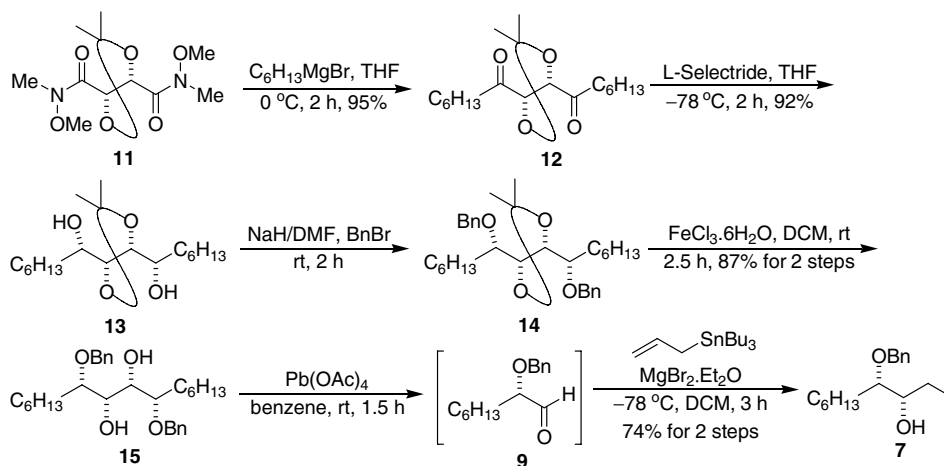
Scheme 1. Retrosynthesis of (–)-microcarpalide **1**.

Keywords: Decanolide; Microcarpalide; Stereoselective reduction; Tartaric acid.

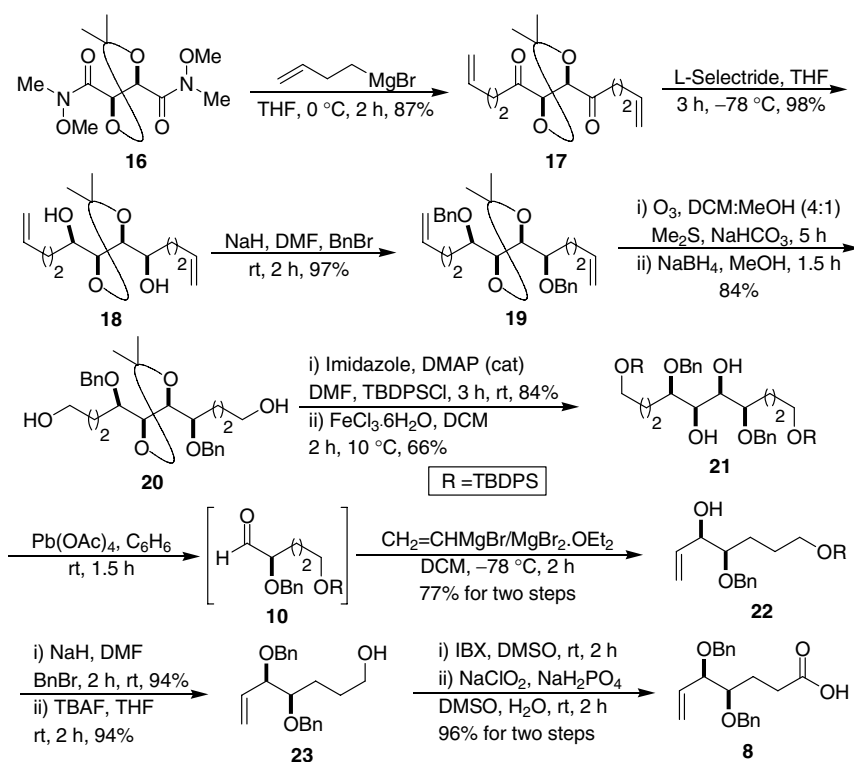
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Continuing efforts from our laboratory on enantioselective synthesis of natural products from chiral pool tartaric acid has resulted in the synthesis of a number of bio-active pheromones and styryl lactones.³ A pivotal step in our approach is the enantioselective synthesis of α -benzyloxy aldehydes, which serve as excellent synthons for further elaboration. We envisaged the synthesis of (–)-microcarpalide **1** through the key precursor **5**, which in turn can be derived from the RCM reaction of diene ester **6**. Assembly of the alcohol and acid components **7** and **8** of the diene ester was envisaged from aldehydes **9** and **10**, which can be derived from D- and L-tartaric acid, respectively (Scheme 1).

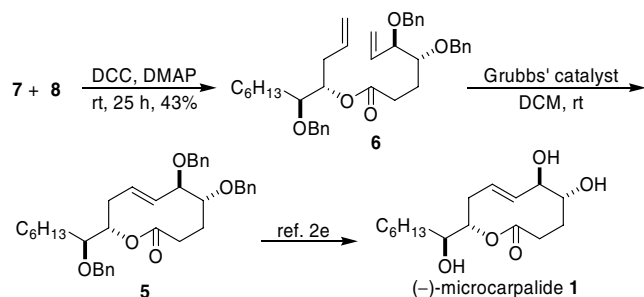
The synthetic sequence for alcohol component **7** commenced with the addition of *n*-hexylmagnesium bromide to bis-Weinreb amide **11**⁴ derived from D-(–)-tartaric acid affording diketone **12** in a 95% yield. Under conditions optimized by us for the reduction of these types of diketones,⁵ the reduction of **12** with L-Selectride furnished a single diastereomer of 1,4-diol **13** in a 92% yield. Subsequent protection of diol **13** under standard conditions afforded dibenzyl ether **14**. Facile deprotection of the acetonide⁶ in **14** was accomplished with FeCl₃·6H₂O to yield diol **15** in a 87% yield. Treatment of diol **15** with Pb(OAc)₄ furnished aldehyde **9**, which on subsequent allylation under Keck allylation conditions⁷



Scheme 2. Synthesis of homoallylic alcohol **7**.



Scheme 3. Synthesis of 6-heptenoic acid fragment **8**.



Scheme 4. Synthesis of (–)-microcarpalide 1.

with allyltributyltin furnished the required *threo* alcohol **7** as the sole diastereomer ($[\alpha]_D +17.1$ (c 1.7, CHCl_3), lit.^{2c} $[\alpha]_D +17.4$ (c 1.5, CHCl_3)) (Scheme 2).

Synthesis of the olefinic acid fragment **8** was initiated by the addition of 3-butenylmagnesium bromide to bis-Weinreb amide **16**⁴ derived from L-(+)-tartaric acid to yield diketone **17** in an 87% yield. L-Selectride reduction of diketone **17** afforded diol **18** as a single diastereomer in a 98% yield. Alcohol **18** was converted to dibenzylether **19**, which on ozonolysis followed by reduction with NaBH_4 afforded diol **20** in an 84% yield. The primary alcohol groups in **20** were protected as the corresponding *tert*-butyldiphenylsilyl (TBDPS) ethers. Next, a facile deprotection of the acetonide with $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ ⁶ furnished diol **21**. Treatment of diol **21** with $\text{Pb}(\text{OAc})_4$ resulted in aldehyde **10**, which on reaction with vinylmagnesium bromide in the presence of $\text{MgBr}_2 \cdot \text{OEt}_2$ in dichloromethane produced *threo* alcohol **22** as a single diastereomer.⁸ Protection of the secondary alcohol group in **22** as benzyl ether and deprotection of the silyl ether afforded **23** in a high yield. Oxidation of the primary alcohol with IBX gave the aldehyde, which on further oxidation with NaClO_2 yielded acid **8** in a 96% yield. The spectral data and the physical properties ($[\alpha]_D +16.6$ (c 0.9, CHCl_3), lit.^{2h} $[\alpha]_D +16.8$ (c 0.7, CHCl_3)) of acid **8** were in complete agreement with those reported in the literature (Scheme 3).

After successfully obtaining the alcohol and acid fragments, the synthesis of (–)-microcarpalide via ester **6**, employing the procedure reported by Davoli et al.^{2e} was undertaken. Accordingly, DCC/DMAP mediated coupling of alcohol **7** with acid **8** generated ester **6** ($[\alpha]_D +2.0$ (c 2.0, CHCl_3), lit.^{2e} $[\alpha]_D +1.9$ (c 1.4, CHCl_3)), which on ring closing metathesis (RCM) with Grubbs 1st generation catalyst in dichloromethane produced **5**. Interestingly, RCM reaction using Grubbs 2nd generation catalyst produced an *E/Z* mixture of decanolide **5** in a 33% yield with 64% of unreacted starting com-

pound. Since the conversion of **5** to (–)-microcarpalide has already been reported in the literature, the present sequence constitutes a formal total synthesis (Scheme 4).

Acknowledgements

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