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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.

(−)-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.

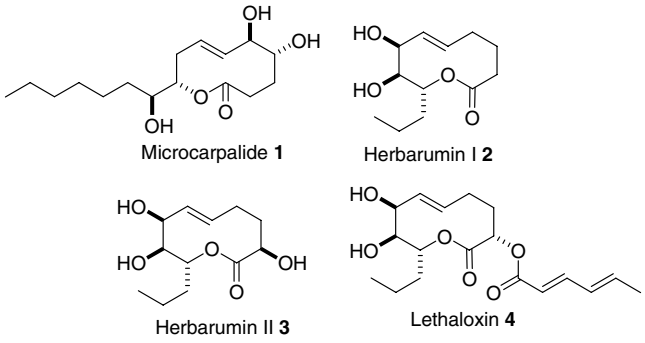
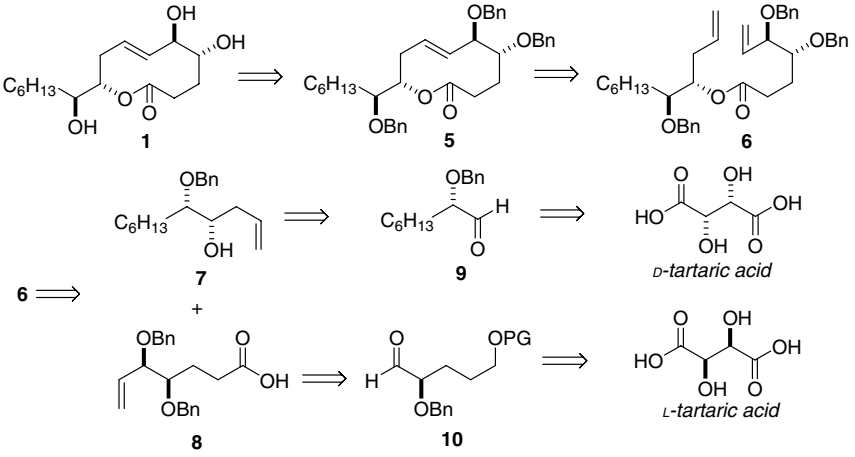


Figure 1. Bioactive fungal decanolactones.



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

Keywords: Decanolide; Microcarpalide; Stereoselective reduction; Tartaric acid.
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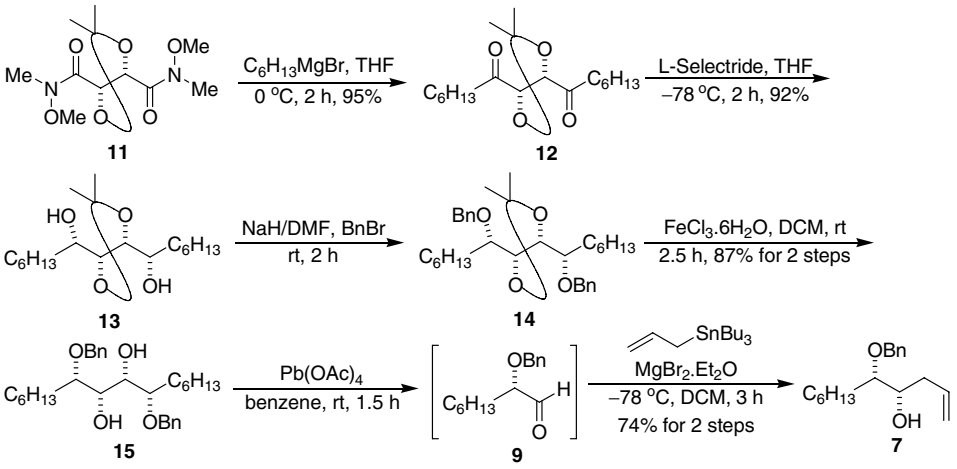
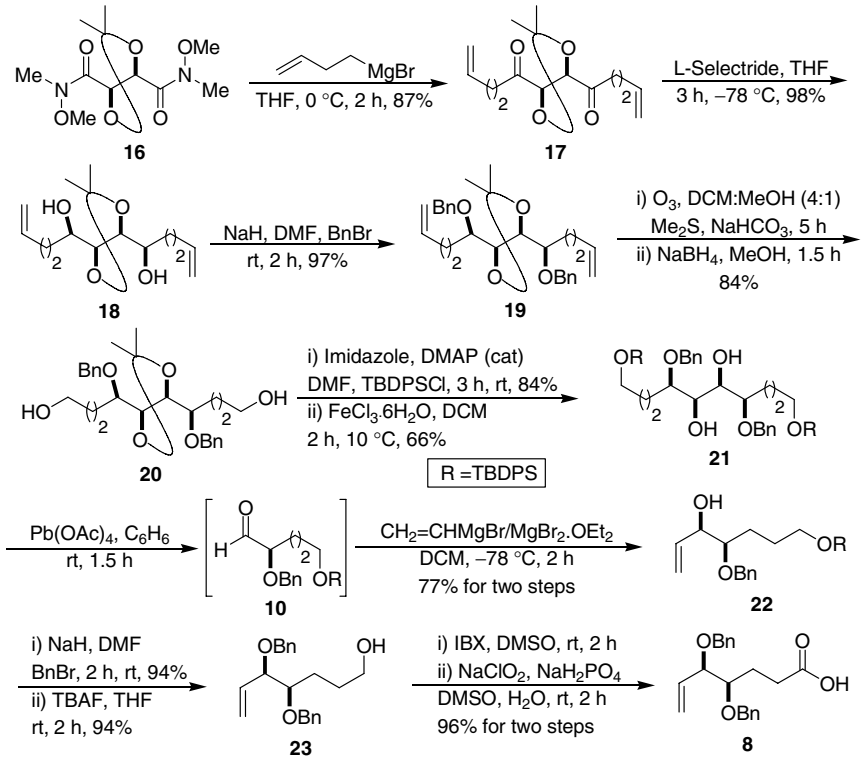
Continuing efforts from our laboratory on enantioselective synthesis of natural products from chiral pool tartaric acid has resulted in the synthesis of a number of bio-active pheromones and styryl lactones.[3] A pivotal step in our approach is the enantioselective synthesis of α-benzyloxy aldehydes, 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).

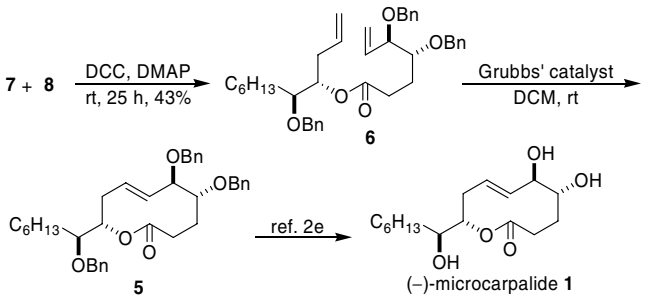
The synthetic sequence for alcohol component **7** commenced with the addition of *n*-hexylmagnesium bromide to bis-Weinreb amide **11**[4] derived from D-(−)-tartaric acid affording diketone **12** in a 95% yield. Under conditions optimized by us for the reduction of these types of diketones,[5] the 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 acetonide[6] in **14** was accomplished with $FeCl_3{\cdot}6H_2O$ 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 conditions[7]



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.[2e] $[\alpha]_D$ +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 dibenzyl-ether **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 $FeCl_3{\cdot}6H_2O$[6] furnished diol **21**. Treatment of diol **21** with $Pb(OAc)_4$ resulted in aldehyde **10**, which on reaction with vinyl magnesium bromide in the presence of $MgBr_2{\cdot}OEt_2$ 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. Accordingy, 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 compound. 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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