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SYNTHESIS OF MICROCARPALIDE, A MICROFILAMENT DISRUPTING AGENT

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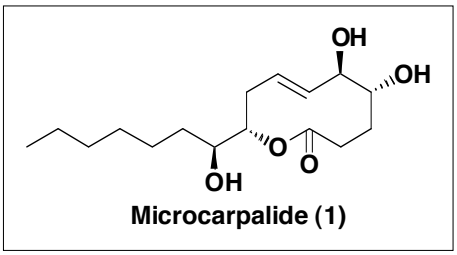
Abstract – Microcarpalide is a strong microfilament disrupting agent. The convergent and stereoselective synthesis of microcarpalide was succeeded *via* Julia olefination and macrolactonization.

INTRODUCTION

Microcarpalide, a ten-membered lactone, was isolated from the fermentation broth of an unidentified endophytic fungus by Hemscheidt and co-workers in 2001.[1] This compound acts as a strong microfilament disrupting agent and shows weak cytotoxicity to mammalian cells. Because of the large difference between the effective concentration for the antimicrofilament activity and the cytotoxicity, it is thought that this compound will be an effective tool for the studies of cell motility and metastasis. Then, we started the synthesis of microcarpalide.

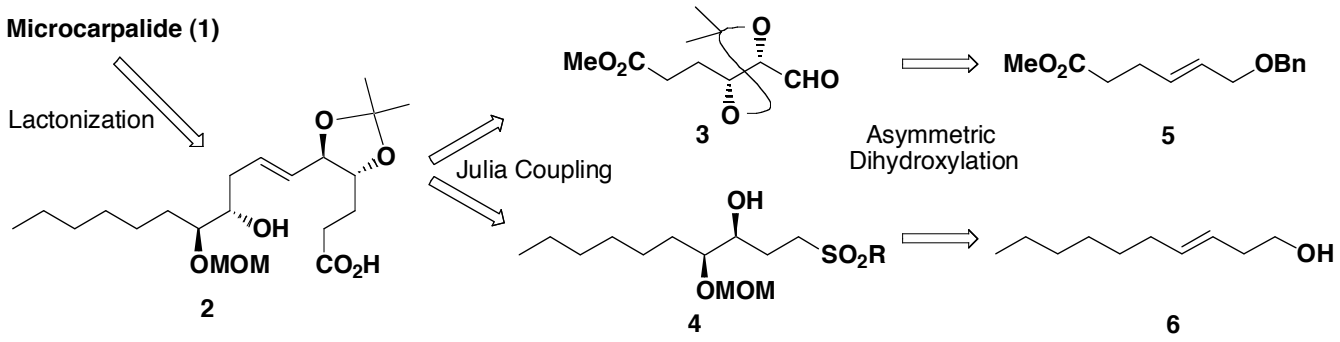


Microcarpalide (1)

Figure 1

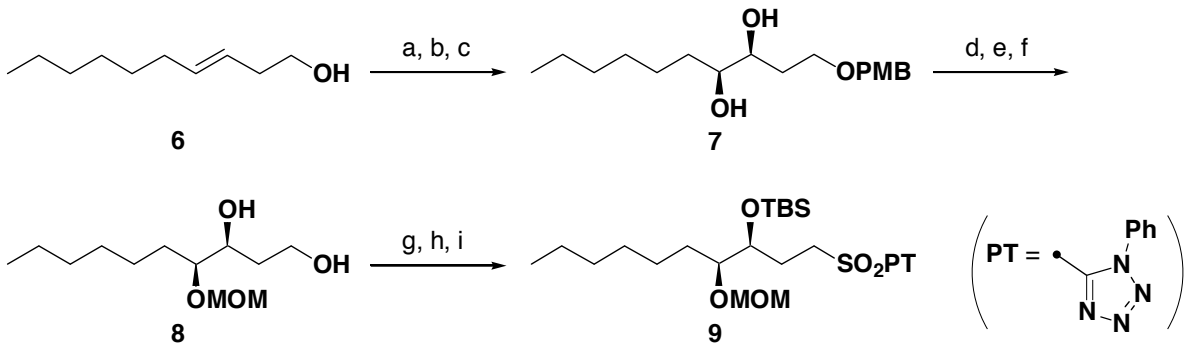
RESULTS AND DISCUSSION

Our retrosynthesis is shown in Scheme 1. We selected lactonization as a ring closing step. The precursor for the lactonization (**2**) would be prepared from aldehyde (**3**) and sulfone (**4**) *via* one-pot Julia coupling.[2] The aldehyde and the sulfone would be obtained by Sharpless asymmetric dihydroxylation[3] of olefins (**5** and **6**), respectively. During our work in progress, Marco *et al.*[4] and Gurjar *et al.*[5] also reported the total synthesis of microcarpalide, both using ring closing metathesis as a key step.



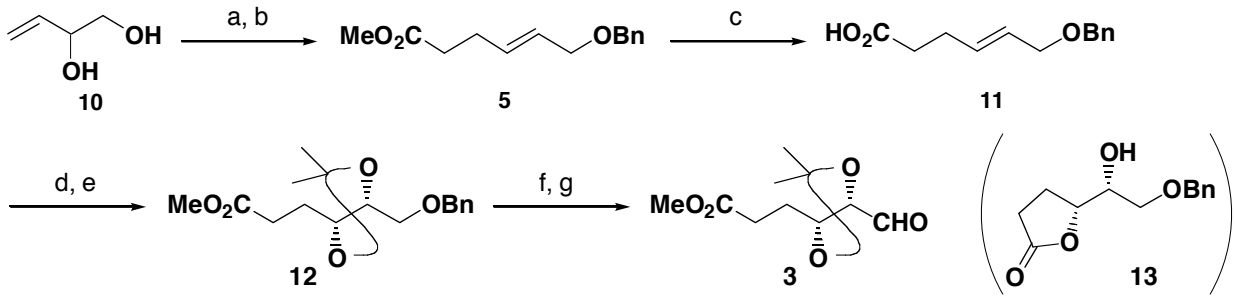
Scheme 1

The synthesis of the sulfone unit is shown in Scheme 2. The known olefinic alcohol (**6**)[6] was protected with PMB group and subjected to Sharpless asymmetric dihydroxylation[3,7] to give diol (**7**, 95% e.e.) as colorless crystal. The purification of this enantiomers (**7**) could be realized by two times of recrystallization, affording **7** with >99% e.e. (checked by chiral HPLC). This diol was converted to *p*-methoxybenzylideneacetal and the residual secondary alcohol was protected by MOM group. After removal of *p*-methoxybenzylideneacetal, the primary hydroxyl group of **8** was converted to corresponding 1-phenyl-1*H*-tetrazol-5-yl sulfone[8] by Mitsunobu reaction and subsequent Mo(VI) catalyzed oxidation.[9] Preparation of the sulfone unit (**9**) was achieved by protection of the secondary alcohol.



Scheme 2. a) PMBCl, NaH, TBAB, THF, reflux, quant. b) AD-mix-α, *t*-BuOH, H_2O, 95% e.e. c) recrystn., >99% e.e., 74% in 2 steps. d) DDQ, CH_2Cl_2. e) MOMCl, *i*-Pr_2EtN, CH_2Cl_2. f) AcOH, H_2O, THF, 81% in 3 steps. g) PTSH, PPh_3, DIAD, THF. h) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, H_2O_2, EtOH. i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 91% in 3 steps.

On the other hand, synthesis of the aldehyde unit (**3**) is shown in Scheme 3. Started from diol (**10**)[10], olefinic ester (**5**) was synthesized by Claisen rearrangement.[11] Direct dihydroxylation of **5** gave exclusively γ-lactone (**13**) instead of desired diol. This lactone could be converted to **12** *via* methanolysis and protection, but the yield was low (<40% in 3 steps). Thus, ester (**5**) was temporarily hydrolyzed into carboxylic acid (**11**), which was subjected to Sharpless asymmetric dihydroxylation[3] to afford the desired diol. This unstable diol was protected immediately together with re-esterification of the carboxyl group to give **12**. In order to determine the enantioselectivity of this dihydroxylation, **12** was treated with TsOH to afford γ-lactone (**13**), which was converted to corresponding (*R*)- and (*S*)-Mosher's esters.[12] The stereochemistry was confirmed by modified Mosher's method[13] and the enantiomeric purity of this compound was determined to be 60% e.e. by ^{1}H-NMR spectrometry. Compound (**12**) was oxidized to the corresponding aldehyde mediated by oxoammonium salt[14] successfully. This aldehyde was thought to have 60% e.e., but it was used in the next step without further purification.

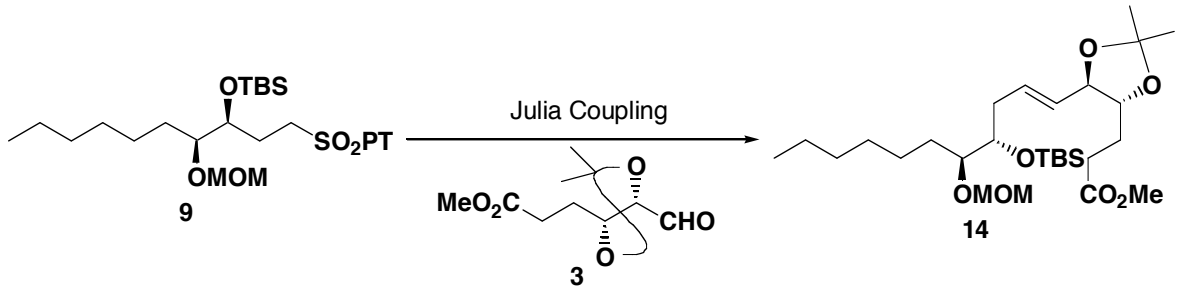


Scheme 3. a) BnBr, NaH, TBAI, THF. b) $MeC(OMe)_3$, $EtCO_2H$, 140°C, 48% in 2 steps. c) LiOH, THF, H_2O, 95%. d) AD-mix-β, *t*-BuOH, H_2O. e) 2,2-dimethoxypropane, HCl, acetone, 74% in 2 steps. f) H_2, 10% Pd / C, *i*-PrOH, 91%. g) 4-MeO-TEMPO, KBr, NaOCl, $NaHCO_3$, CH_2Cl_2, H_2O, 70%.

Now that both of two units were obtained, we tried one-pot Julia coupling[2,8,15] in several conditions (Table 1). The reaction using LiHMDS as base gave desired olefin (**14**) in poor yield (Entries 1 and 2). On the other hand, good yield was realized when KHMDS was used as base, but *E*/*Z* selectivity was not so high (Entries 3 and 4). Because it seemed that this low *E*/*Z* selectivity was caused by the chelation of oxygen functional groups in the sulfone (**9**) and the aldehyde (**3**) to potassium cation, we tried other conditions using additives to prevent this chelation. When 18-c-6 was used as an additive (Entry 6), *trans*-olefin (**14**) was obtained successfully in good yield and high selectivity. Although *trans*-**14**, which was easily separated from *cis*-**14**, was the diastereomeric mixture (4 : 1) resulting from the inadequate enantiomeric purity of aldehyde (**3**), this mixture was used in the next step without further separation.

Final steps including lactonization are shown in Scheme 4. The *trans*-olefin (**14**) was treated with TBAF and hydrolyzed to give a lactonization precursor (**2**). Hydroxy acid (**2**) was subjected to lactonization

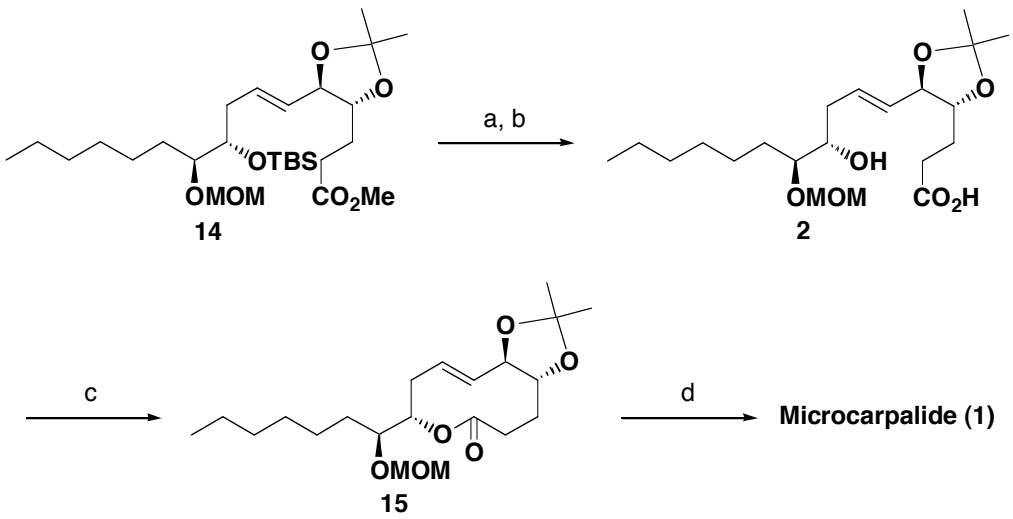
using Yamaguchi's method[16] to afford ten-membered lactone in quantitative yield as a diastereomeric mixture without formation of its dimer. These diastereomers were easily separated by silica gel chromatography and the desired lactone (**15**, 77%) and its diastereomer (20%) were obtained. Deprotection of **15** was performed in the same method as Marco *et al.*[4] and synthesis of microcarpalide (**1**) was achieved successfully. The analytical and spectroscopic data[17] of synthesized **1** were identical to the reported data.[1,4,5]



Entry	Base	Temp.	Additive	*E* : *Z*	Yield
1	LiHMDS	–78°C	-	3 : 1	10%
2	LiHMDS	–108°C	-	10 : 1	32%
3	KHMDS	–78°C	-	2 : 1	64%
4	KHMDS	–108°C	-	2 : 1	77%
5	KHMDS	–108°C	HMPA	3 : 1	71%
6	KHMDS	–108°C	18-c-6	10 : 1	72%

Solvent: THF

Table 1



Scheme 4. a) TBAF, THF, 99%. b) LiOH, H_2O, THF, quant. c) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, benzene, 77% (**15**), 20% (diastereomer). d) $BF_3{\cdot}OEt_2$, $(CH_2SH)_2$, CH_2Cl_2, 69%.

In conclusion, we have accomplished a convergent and stereoselective synthesis of microcarpalide via an asymmetric dihydroxylation, one-pot Julia olefination and Yamaguchi's macrolactonization. The application of aldehyde (**3**) which has higher enantiomeric purity will enhance the total yield of this synthesis. Work is under way to refine every step of synthesis and the result will be reported in a full account.

ACKNOWLEDGEMENTS

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17. Spectral data of synthesized **1**: ^{1}H-NMR (300 MHz, CD_3CN, observed as a mixture of two conformers in the ratio 3-4 : 1.) *Major conformer*; δ (ppm) 0.88 (3H, t, *J* = 6.9 Hz), 1.2-1.4 (8H, m), 1.3-1.5 (2H, m), 1.7-1.8 (1H, m), 2.0-2.2 (2H, m), 2.1-2.3 (2H, m), 2.4-2.6 (1H, m), 2.8-2.9 (2H, br m), 3.12 (1H, br d), 3.54 (1H, br m), 3.77 (1H, br), 4.10 (1H, br), 4.81 (1H, ddd, *J* = 3.3, 4.8, 11.1

Hz), 5.49 (1H, dddd, *J* = 2.1, 5.1, 9.9, 15.6 Hz), 5.69 (1H, dd, *J* = 2.4, 15.6 Hz). *Minor conformer*; δ (ppm) 0.88 (3H, t, *J* = 6.9 Hz), 1.2-1.4 (8H, m), 1.3-1.5 (2H, m), 1.7-1.8 (1H, m), 2.0 (1H, m), 2.0-2.2 (1H, m), 2.2-2.4 (1H, m), 2.4-2.6 (2H, m), 2.8-2.9 (2H, br m), 3.2-3.3 (2H, br m), 3.5-3.6 (2H, m), 4.60 (1H, ddd, *J* = 2.7, 4.5, 8.1 Hz), 5.05 (1H, dd, *J* = 9.3, 15.6 Hz), 5.6-5.7 (1H, m). ^{13}C-NMR (75 MHz, CD_3CN, observed as a mixture of two conformers.) δ (ppm) 14.4, 23.3, 26.1, 26.3, 26.3, 26.4, 29.0, 29.9, 32.1, 32.2, 32.5, 33.8, 34.1, 35.9, 36.7, 72.4, 72.8, 73.4, 73.8, 76.4, 76.9, 79.5, 79.7, 126.6, 130.0, 133.7, 134.5, 173.5, 176.4. $[\alpha]_D^{26}$ –29° (*c* 0.67, MeOH). n_D^{19} 1.4965. ESI-HRMS *m*/*z* calcd for $C_{16}H_{28}NaO_5$ $[M+Na]^+$ 323.1834, found 323.1843.