SYNTHESIS OF BOTH ENANTIOMERS OF ACETOPHTHALIDIN

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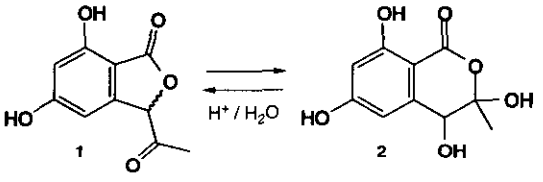
Abstract —Both enantiomers of acetophthalidin, a potent cell cycle inhibitor, were synthesized employing Sharpless asymmetric dihydroxylation as a key step.

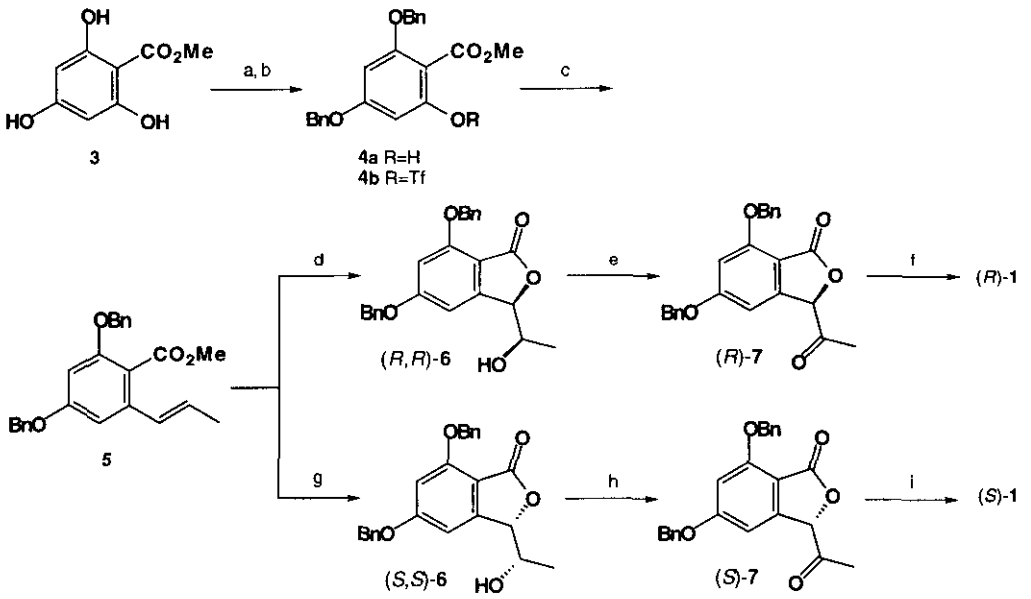
In 1996, Osada *et al.* isolated acetophthalidin (**1**) from a culture broth of a fungal strain BM923.[1] This simple phenolic lactone shows a potent inhibitory activity to the cell cycle progression of the mouse tsFT210 cells in the M phase. Due to the instability of **1**, however, it has isomerized readily to inactive trihydroxymellein (**2**) during the isolation and was obtained only as a racemate by heating the isolated **2** under acidic condition. This nature as well as its strong activity made us to synthesize both enantiomers of **1** to clarify the difference of their activities.[2]



We started from methyl phloroglucinolcarboxylate (**3**).[3] Benzylation of **3** using 2.1 eq. of benzyl bromide gave its 2,4-dibenzyl ether (**4a**) as a major product (47%, mp 117.0 °C) (Scheme 1). The dibenzyl ether (**4a**) was treated with trifluoromethanesulfonic anhydride to give **4b** as colorless needles (mp 95.0~95.5 °C, 77%). Coupling of **4b** with excess tri-*n*-butyl-1-propenyltin (1:1 *E* / *Z* mixture)[4] under Stille's conditions[5] afforded a mixture of (*E*)- and (*Z*)-olefin (**5**) (3:1 by ^{1}H NMR), which on recrystallization from hexane / ethyl acetate gave almost pure (*E*)-isomer (50:1, 59%, mp 101.0~102.0 °C). Asymmetric dihydroxylation of **5** with AD-mix-β[6] gave optically active hydroxylactone (*R*, *R*)-**6** of 99.7%e.e.(by HPLC[7]), which was recrystallized to give pure (*R*, *R*)-**6** with ~100%e.e. ($[\alpha]^{19}_{D}$ –40° (*c* 1.2, MeOH), mp 122.0~123.5 °C).

The next oxidation step was critical because we had to optimize the procedure to avoid racemization and/or isomerization to trihydroxymellein derivative. Thus, we selected Dess-Martin oxidation[8] or two-phase Jones oxidation[9] to oxidize the *sec*-hydroxyl group of (*R*, *R*)-**6** because the reaction was fast and (*R*)-**7** was obtained as a single product. When PCC or PDC was used, the reaction became slower and

undesired isomerization to trihydroxymellein derivative occurred. It was unsuccessful to determine its enantiomeric purity directly by HPLC with several columns with optically active stationary phase. We then tried the following method (Scheme 2). Reduction of (*R*)-**7** with lithium tri-*t*-butoxyaluminohydride in THF afforded a mixture of (*R*, *R*)-**6** and (*R*, *S*)-**6**, and the enantiomeric purity of (*R*, *R*)-**6** was determined by HPLC.[7] It seemed partial racemization occurred during the oxidation (or the reduction), that is, two-phase Jones oxidation gave (*R*)-**7** with 87.0%e.e., while Dess-Martin oxidation gave that with 89.7%e.e.

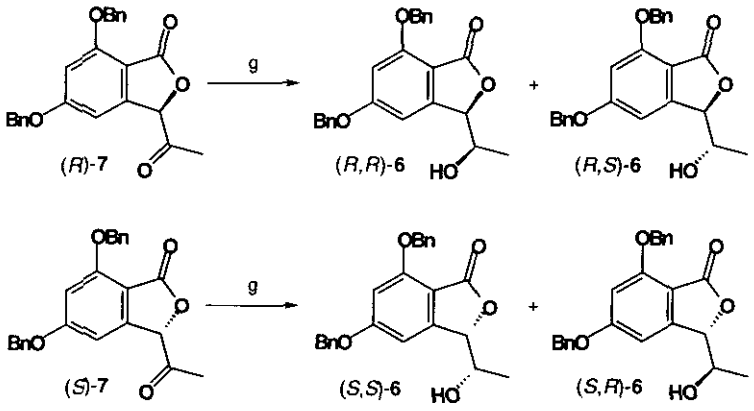


Scheme 1 ; a) BnBr (2.1 eq.), K_2CO_3, NaI, DMF, rt, 12 h, 47%. b) Tf_2O, pyridine, CH_2Cl_2, –40 °C, 0.5 h; 0 °C, 3.5 h, 77%. c) MeCH=CHSnBu^n_3 (*EZ* mixture, 1.7 eq.), Pd(0)[PPh_3]$_4$, LiCl, THF, 90 °C, 7 d; recryst'n, 59%. d) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 4 °C, 12 d; recryst'n, 75%. e) Dess-Martin reagent, CH_2Cl_2, rt, 1 h, 91%. f) H_2, 10% Pd(OH)$_2$-C, AcOEt, rt, 15 min, 71%. g) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH, H_2O, 4 °C, 3 d; recryst'n, 79%. h) Dess-Martin reagent, CH_2Cl_2, rt, 1 h, 99.5%. i) H_2, 10% Pd(OH)$_2$-C, AcOEt, rt, 15 min, 87%.

The crude (*R*)-**7** obtained by Dess-Martin oxidation was immediately recrystallized from hexane / ethyl acetate without heating to give pure (*R*)-**7** as a colorless fine needles, whose mp was 135.0~137.0 °C (91% yield, $[\alpha]^{22}_D$ +171° (*c* 0.95, $CHCl_3$)). Finally, benzyl groups were hydrogenolyzed using large amount of 10% Pd(OH)$_2$-C in ethyl acetate in less than 15 min to give (*R*)-**1** which was immediately reprecipitated as a colorless powder (71%). The mp was 189.0~201.0 °C (decomp) and the specific rotation was $[\alpha]^{20}_D$ +23° (*c* 0.89, EtOAc). ^{1}H NMR spectrum and IR spectrum data were identical with those in the literature.[1, 10]

In the same manner, (*S*)-**1** was synthesized. Asymmetric dihydroxylation of **5** with AD-mix-α[6] gave (*S*, *S*)-**6** of 99.3%e.e.(by HPLC[7]), which was recrystallized to give (*S*, *S*)-**6** with ~100%e.e.(79% yield). Its mp was 121.5~122.0 °C, and its specific rotation was $[\alpha]^{21}_D$ +41° (*c* 1.4, MeOH)). Dess-Martin oxidation

of (*S*, *S*)-**6** afforded (*S*)-**7** which was recrystallized at low temperature to give pure (*S*)-**7** in 99.5% yield (mp 133.0~135.0 °C, $[\alpha]^{19}_{D}$ −166° (*c* 1.3, $CHCl_3$)). Enantiomeric purity of (*S*)-**7** determined in the same procedure (Scheme 2) was 92.7%e.e. Then it was hydrogenated similarly to give (*S*)-**1** which was immediately reprecipitated as a colorless powder (87%). Its mp was 190.0~201.0 °C (decomp) and its specific rotation was $[\alpha]^{20}_{D}$ −27° (*c* 0.72, EtOAc). ^{1}H NMR spectrum and IR spectrum data were identifcal with those of (*R*)-**1**.



Scheme 2 ; g) Li(*t*-BuO)$_3$AlH, THF, −30 °C, 1 h

In conclusion, we synthesized the both enantiomers of acetophthalidin in 6 steps starting from **3**. The overall yield was 10.3% for (*R*)-**1** and 14.6% for (*S*)-**1**. As described in the literature, the synthetic **1** was also very unstable ($T_{1/2}$ of $[\alpha]_D$ was 33 min in MeOH at 22 °C), and against our expectation, the both enantiomers showed no difference of activity in bioassay. Detailed study on the synthesis and biological activities of related analogues are in progress and the results will be reported in a full account.

ACKNOWLEDGEMENT

We thank Dr. H. Osada, RIKEN, The Institute of Physical and Chemical Research, for kind gift of the spectra of acetophthalidin and for bioassay.

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10. IR (KBr): ν = 3310, 3170, 1720, 1620, 1480, 1360, 1330, 1230, 1200, 1160, 1050, 760, 700 cm^{-1}; ^1H NMR (500 MHz in DMSO-d_6): δ = 2.08 (3H, s, $-CH_3$), 5.80 (1H, br s, 3-H), 6.27 (1H, d, 1.8 Hz, Ar-H), 6.29 (1H, m, Ar-H), 10.48 (1H, br s, Ar-OH), 10.67 (1H, br s, Ar-OH).

Received, 12th February, 1997