SYNTHESIS OF (+)-IPOMEAMARONE

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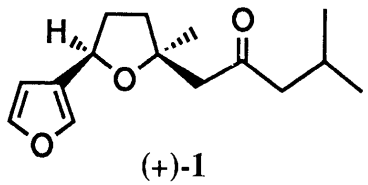
(+)-Ipomeamarone (**1**), a furanosesquiterpene isolated from the mold-damaged sweet potato *Ipomea batatas* as one of the phytoalexins, was synthesized starting from (+)-lactic acid as a chiral source.

KEY WORDS (+)-ipomeamarone; furanosesquiterpene; chiral self-reproduction; (+)-lactic acid; phytoalexin

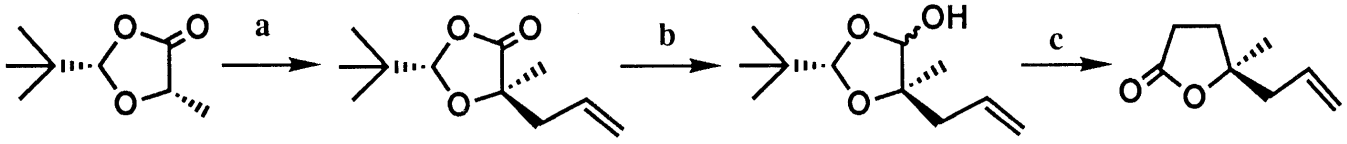
In the course of our synthetic studies on the biologically active natural products, which have a chiral quaternary carbon substituted by one oxygen, we reported the synthesis of (-)-frontalin and (-)-malyngolide.[1] In this communication, we describe the total synthesis of (+)-ipomeamaro-ne (**1**), which is a furanosesquiterpene isolated from the mold-damaged sweet potato *Ipomea batatas* as one of the first phytoalexins by Hiura. [2] The structure of ipomeamarone was elucidated by Kubota and Matsuura,[3] and its absolute stereochemistry was determined by Nakanishi *et al.* [4] in 1983. Four synthetic studies of racemic ipomeamarone (**1**) [5] and two of (+)-**1** [6] have been published so far.



(+)-1

Our synthetic work on (+)-ipomeamarone (**1**) started with the preparation of chiral lactone (+)-(**5**), which is a useful compound for the introduction of both the furyl group and the side chain existing in **1**.

Seebach [7] reported the synthesis of the dixolanone (+)-(**3**) by stereospecific allylation of (+)-**2**, which was prepared by the condensation of 2,2-dimethylpropanal and (+)-lactic acid through " chiral self-reproduction". The dioxolanone (+)-(**3**) was reduced by diisobutylaluminum hydride (DIBAL-H) in CH_2Cl_2 to the dioxolanol (**4**) in 97% yield. Wittig-Horner reaction of **4** with trimethyl phosphonoacetate in the presence of NaH in THF and subsequent selective reduction of the formed α,β-unsaturated double bond with potassium tri-*sec*-butylborohydride (K-selectride) in the presence of the terminal double bond gave the desired lactone (+)-(**5**) [8] after acidic workup in 47% yield from **4**.



(+)-2 (+)-3 4 (+)-5

a) Ref 7. b) DIBAL-H in CH_2Cl_2, -78 °C (97%). c) i) $(MeO)_2P(O)CH_2COOMe$, NaH in THF, rt ii) K-Selectride in THF, -78 °C-rt; 10% NaOH, 30% H_2O_2, rt; iii) 10% HCl, 50 °C, 30 min (47% from 4).

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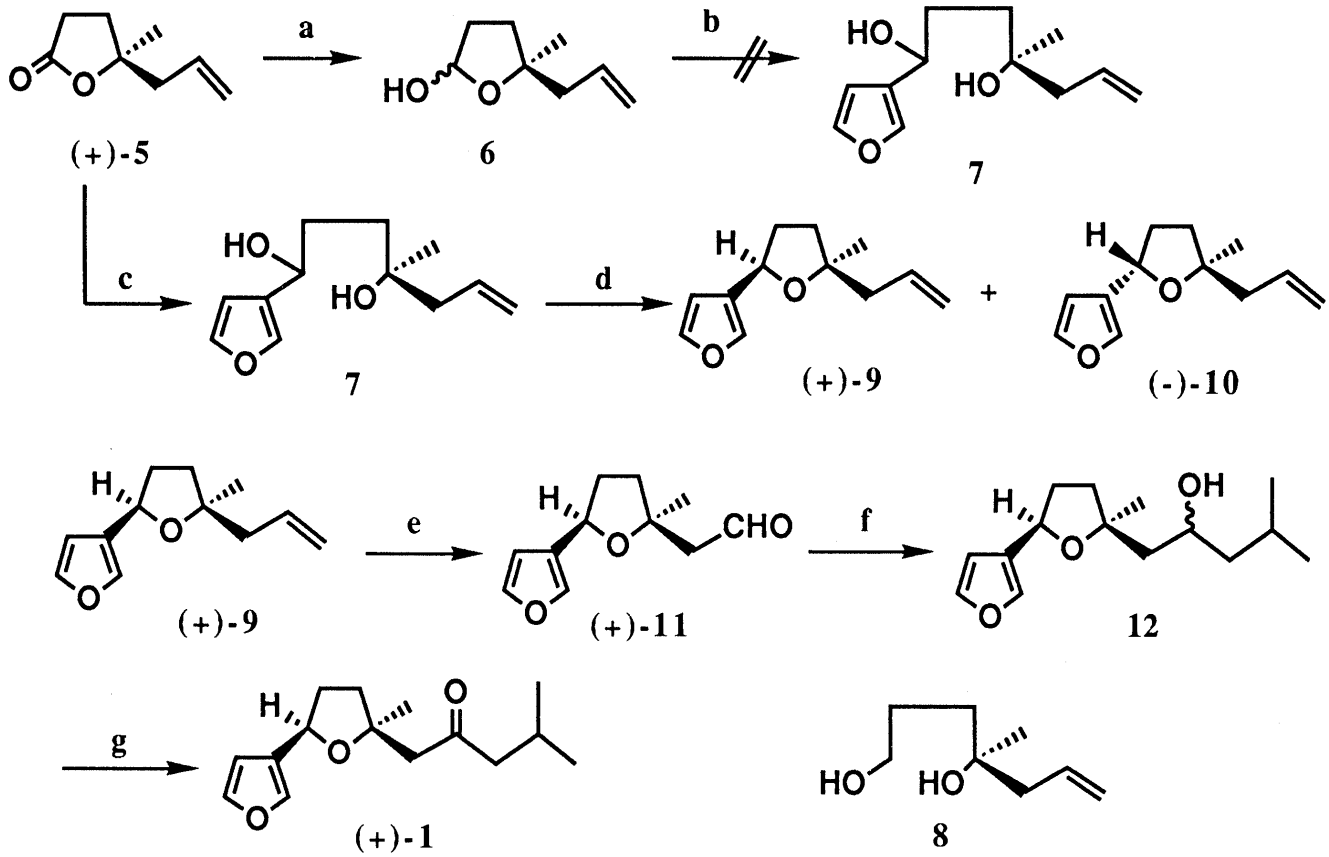
As the lactone (+)-(**5**) was in our possession, we next examined the introduction of the furyl group. When 3-furyllithium [9] was reacted with the lactol (**6**), which was obtained by DIBAL-H reduction of (+)-**5** in 78% yield, the expected diol (**7**) was not obtained and the lactol (**6**) was recovered. One of us has encountered a similar unreactivity of the lactol with 3-furyllithium in the synthesis of poltural.[10]



a) DIBAL-H in CH_2Cl_2 (78%). b) 3-furyllithium in ether. c) i) 3-furyllithium (1.5 eq), -78 °C, 2.5 h; ii) $LiAlH_4$ (1 mol), -78°C-rt, 17 h. d) i) *p*-TsCl, pyridine; ii) SiO_2 separation (AcOEt:hexane=1:29). e) i) OsO_4-NMO in CH_3CN-H_2O; ii) $NaIO_4$, 1M $NaHCO_3$ in THF-H_2O (72%). f) isobutylmagnesium bromide in THF (91%). g) PCC-Celite, AcONa in CH_2Cl_2 (86%).

In that case, we overcame the difficulty by the reaction of lactone with 3-furyllithium and then reduction of the formed ketone to the alcohol.[11] When 2.0 eq of 3-furyllithium was added to the ether solution of (+)-**5** at -78°C and stirred for 5.5 hr, and then LiAlH4 was added to the reaction mixture and stirred for 16 hr at room temperature, the desired diol (**7**) was obtained in 46 % yield along with the diol (**8**) in 20% yield, which was the reduction product of (+)-**5**. But when the ether solution of (+)-**5** was added to 3- furyllithium in -78°C and stirred for 2.5 hr, and the subsequent LiAlH4 reduction was carried out, the desired diol (**7**) was obtained in 84% yield and no byproduct was detected. Tosylation of **7** with *p*-toluenesulfonyl chloride (*p*-TsCl) in pyridine gave the cyclization products (+)-**9** ($[\alpha]_D^{24}$ +11.8° *c*=1.14, MeOH) and (-)-**10** ($[\alpha]_D^{24}$ -14.14°, *c*=1.24, MeOH) after SiO_2 column chromatography separation in yields of 25% and 37% from (+)-**5**, respectively. The stereochemistry of (+)-**9** was determined by observation of the NOE between the tertiary methyl group and the methine proton on the tetrahydrofuran ring. Treatment of (-)-**10** with *p*-TsOH in CH_2Cl_2 under reflux gave a mixture of (+)-**9** and (-)-**10** in the ratio of about 3:2.[6b] These results mean that (-)-**10** is also useful for the synthesis of (+)-**1**.

Preparation of the side chain of (+)-**1** was carried out by three-step reaction sequences from (+)-**9**. First, OsO_4-*N*-methylmorpholine *N*-oxide (NMO) oxidation of (+)-**9** in CH_3CN-H_2O and the subsequent $NaIO_4$ oxidation of the formed diol in THF-H_2O keeping the reaction mixture in neutral by addition of 1M $NaHCO_3$ aq solution gave the aldehyde (+)-(**11**) ($[\alpha]_D^{25}$ +12.48°, *c*=1.28, MeOH) in 72% yield. Grignard reaction of (+)-**11** with isobutylmagnesium bromide in THF gave the isomeric mixture of alcohols (**12**) in 91% yield. The mixture was finally oxidized with PCC-Celite in the presence of anhydrous AcONa in CH_2Cl_2 to furnish (+)-ipomeamarone (**1**) in 86% yield; $[\alpha]_D^{25}$ +23.5° (*c*=4.9, EtOH) [lit. [4] $[\alpha]_D$ +27° (*c*=4.7, EtOH)]. The IR and ^{1}H-NMR spectral data of the synthesized (+)-**1** are identical with those of the natural one. [4, 6a]

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