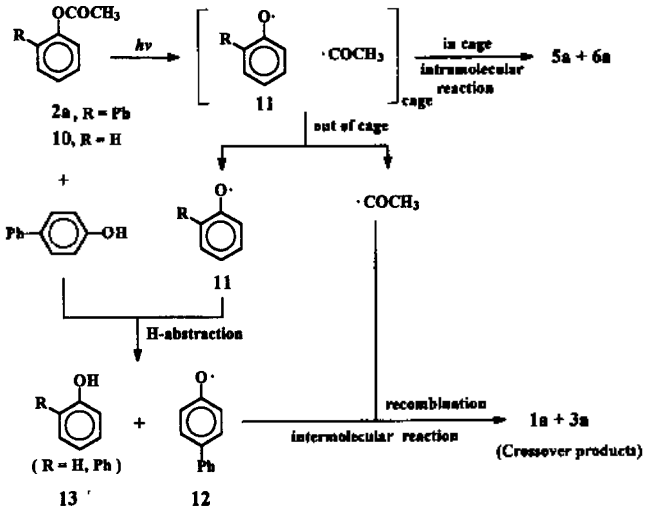
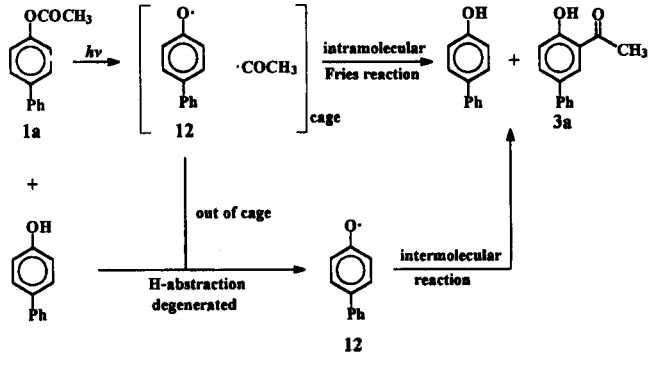


Scheme 3.



Scheme 4.

(Scheme 4).

Though Fries product **3a** would be mostly produced by intramolecular reaction, intermolecular reaction procedure must be considered as a trivial mechanism (Scheme 4).

We are trying to find the optimum reaction condition for better yield of **3a** by trivial mechanism and Fries reaction of phenyl acetate in the presence of deuterated phenol is under investigation to confirm trivial mechanism of photo-Fries reaction.

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5. The mole ratio of the ester to phenylphenol in the irradiation mixture was 4 to 1.
6. Structural identification of the compounds was performed by comparison of NMR spectra with those of authentic samples.

Synthesis of (−)-Macronecine *via* Condensation Reaction between Malate Enolate and Imine

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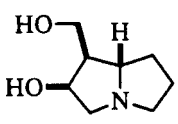
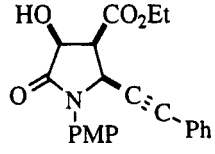
Pyrrolizidine alkaloids, found in the diverse plant species, have long been the targets of many synthetic efforts due to their interesting biological activities with relatively simple structures.[1] Necine bases, having 1-hydroxymethyl group in the pyrrolizidine ring system, compose the majority of the pyrrolizidine alkaloids. Many synthetic methodologies have been developed for the efficient construction of this structure and, mostly, 2-pyrrolidinones have served as useful intermediates for the synthesis of the polyhydroxylated pyrrolizidine alkaloids.

Recently, we reported the diastereoselective condensation between the enolate dianion of diethyl malate and nonenolizable imine and showed diastereoselectivity in the 2-pyrrolidinone formation could be controlled with addition of

HMPA.[2] When the enolate dianion prepared from diethyl (*S*)-malate and two equivalents of $LiN(TMS)_2$ was reacted with phenylpropargylidene-*p*-anisidine in THF-HMPA, the 2-pyrrolidinone **2** was formed in 34% yield with no diastereomer detected. Though the yield of this reaction was disappointingly low, this condensation provided stereoselectively the highly functionalized 2-pyrrolidinone in a single step. Synthesis of (−)-macronecine (**1**), an enantiomer of natural (+)-macronecine, from the 2-pyrrolidinone **2** is described in this communication.[3]



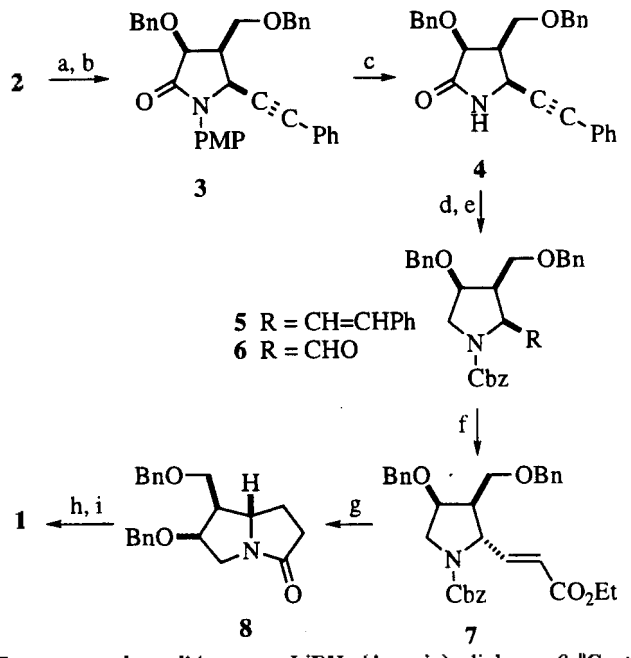
1



2

(PMP=*p*-methoxyphenyl)

The ester **2** was selectively reduced with $LiBH_4$ in diglyme and the resulting diol was bis-benzylated to give **3**. Oxidative dearylation of **3** with ceric ammonium nitrate (CAN) provided **4** in 89% yield. Reduction of the amide and triple bond moieties of **4** with excess of LAH in THF heated at reflux followed by carboxybenzylation of the resulting crude pyrrolidine gave **5** in 95% combined yield. Ozonolysis of **5** (84%) to aldehyde **6** followed by the Wittig reaction gave the unsaturated ester **7** as a 10:1 diastereomeric mixture. The epimerization occured during the Wittig reaction to give the *trans* ester **7** in 84% yield after SiO_2 chromatography. Removal of the Cbz group and reduction of the unsaturated ester of **7** under catalytic hydrogenation provided an aminoester intermediate which was cyclized with $AlMe_3$ to bicyclic amide **8** in 87% combined yield. Hydrogenolysis of the benzyl ethers (95%) of **8** followed by LAH reduction (70%) gave (−)-macronecine (**1**) ($[\alpha]_D^{20} = -41.0$, c 0.19, EtOH) having the identical spectral data (IR, mass, ^1H and ^{13}C NMR) with those reported.[4]



Reagents and conditions. **a.** $LiBH_4$ (4 equiv), diglyme, 0 °C, rt, 20h, 90%; **b.** NaH (2.5 equiv), BnBr (2.5 equiv), DMF, 86%; **c.** CAN (3 equiv), CH_3CN-H_2O (4:1), −23 °C to 0 °C, 89%; **d.** i) LAH (4 equiv), THF, reflux, 3h; ii) CbzCl (1.3 equiv), Et_3N (1.5 equiv), cat. DMAP, THF, rt, 12h, 95%; **e.** O_3, CH_2Cl_2, −78 °C; CH_3SCH_3, 84%; **f.** $Ph_3P{=}CHCO_2Et$, THF, rt, 36h, 84%; **g.** i) 10% Pd-C, H_2 (1 atm), CH_3OH, rt, 1h; ii) $AlMe_3$, toluene, 0 °C, 2h, 87%; **h.** $Pd(OH)_2$, H_2 (1 atm), CH_3OH, rt, 40h, 95%; **i.** LAH (3 equiv), THF, reflux, 10h, 70%.

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