A NEW SYNTHESIS OF (–)-MESEMBRINE EMPLOYING SHARPLESS AD REACTION AND NEW RADICAL-INITIATED REACTION†

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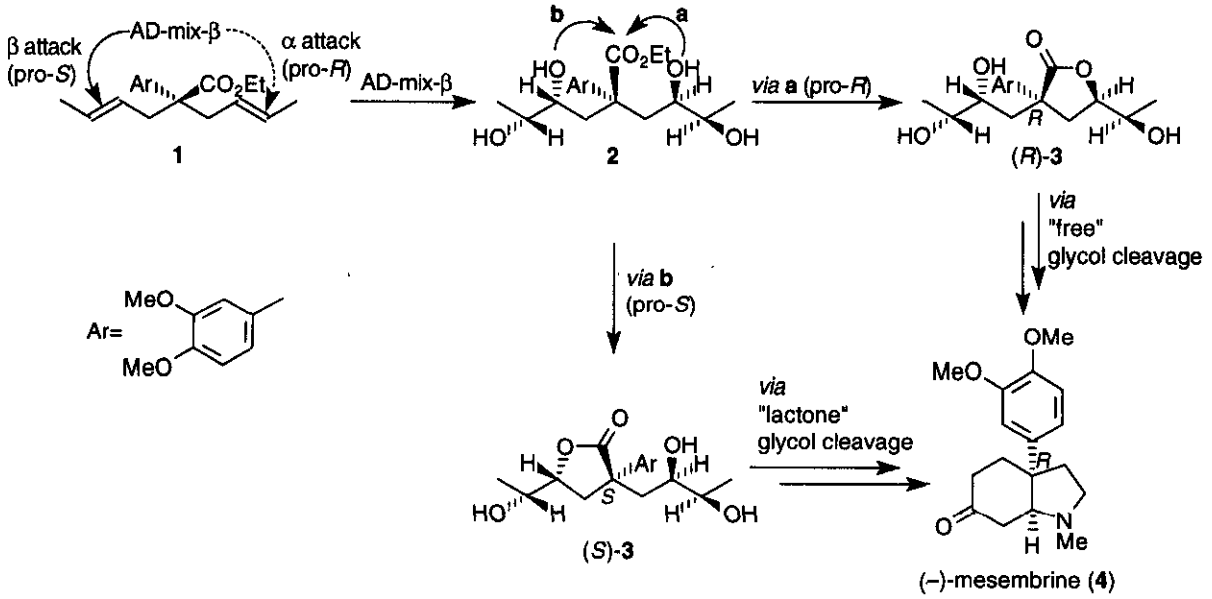
Abstract —— Sharpless asymmetric dihydroxylation (AD reaction) of a σ-symmetric ethyl α,α-di[(*E*)-2-butenyl](3,4-dimethoxyphenyl)acetate allows an asymmetric construction of a quaternary carbon center by diastereoselective formation of the γ-lactone in moderate optical yields when double dihydroxylation occurs. The lactone generated is transformed into a Sceletium alkaloid (–)-mesembrine by discovery of the unprecedented radical-initiated cleavage reaction.

In relation to the first successful application of the Sharpless asymmetric dihydroxylation (AD reaction)[1] to the asymmetrization of a *meso*-symmetric substrate,[2] we investigated the asymmetrization of a σ-symmetric diolefinic substrate having a prochiral quaternary carbon center[3] employing the same reaction. We wish to present here our result which led to an alternative asymmetric synthesis of a Sceletium alkaloid[4] (–)-mesembrine (**4**) in a moderate optical yield *via* a sequence of reactions involving the double AD reaction and the unprecedented radical-initiated reductive cleavage.

Our starting material was σ-symmetric ethyl α,α-di[(*E*)-2-butenyl](3,4-dimethoxyphenyl)acetate[5] (**1**) containing about 6% of the inseparable (*Z*)-olefinic isomers. We assumed first that the reaction of **1** with AD-mix-β reagent should give the single tetraol (**2**) stereoselectively by double AD process by following the empirical rule.[1] We further assumed that the tetraol (**2**) thus generated would spontaneously form a particular one (*R*)-**3**[6] of two possible diastereomeric trihydroxy lactones (*R*)- and (*S*)-**3** by diastereoselective cyclization (*via* **a**) in the most favorable conformation in which the ester and a hydroxy functionalities reside in a proximal position. Moreover, even the stereoselective lactonization would not have occurred, we could still hope the

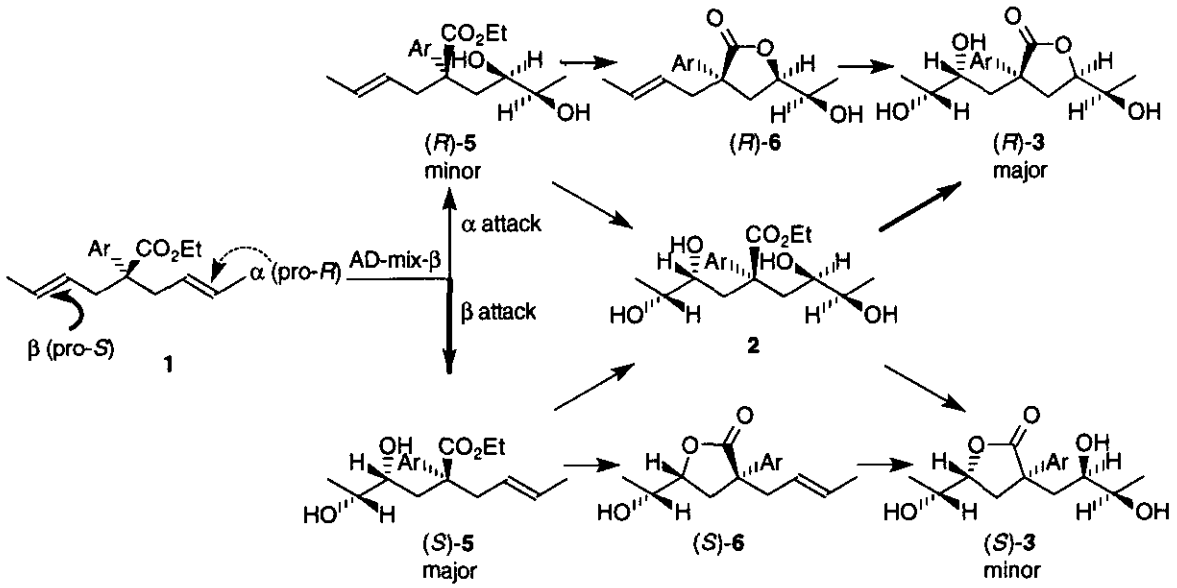
† Dedicated to the memory of Professor Yoshio Ban.

diastereomeric mixture formed to be separable to give diastereomerically pure (*R*)- and (*S*)-**3** both of which could be transformed enantioconvergently into either natural (–)- or unnatural (+)-mesembrine (**4**) based on their latent molecular symmetry by differentiation of the "free" glycol and the "lactone" glycol functionalities (**Scheme 1**).



Scheme 1

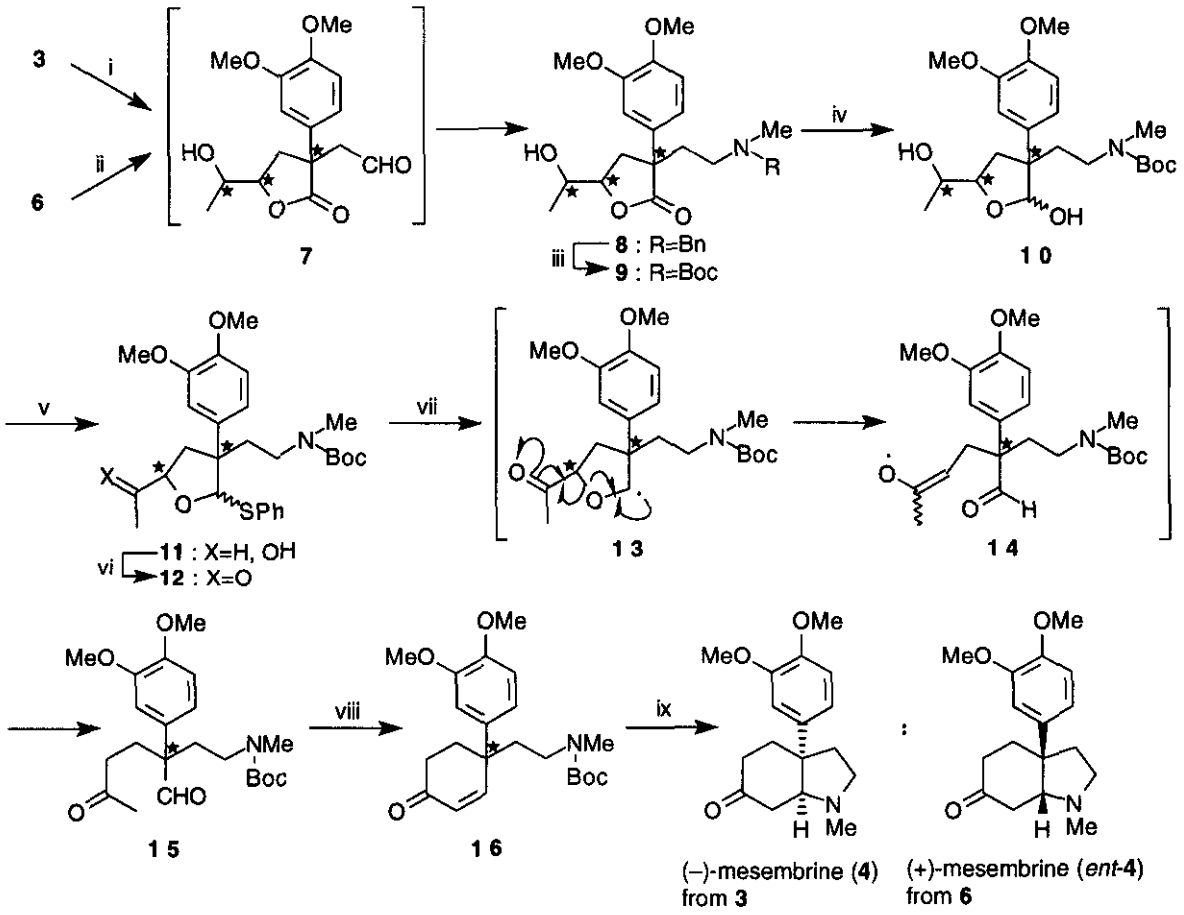
Thus, we first treated **1** with one equivalent[1] of AD-mix-β,[7] which contained three equivalents of potassium ferricyanide(III), in the presence of one equivalent of methanesulfonamide at 0 °C for 140 h to afford two pairs of the diastereomeric lactone mixture, the trihydroxy lactone mixture (**3**) and the ene lactone mixture (**5**), in 54 and 30% yield accompanied by the unreacted starting material (5.4%). Neither the tetraol esters (**2**) nor the diol ester (**6**) was detected under these conditions indicating that facile lactonization occurred both at the single and the double dihydroxylation stages. The reaction could not be terminated at single dihydroxylation stage even though using a limited amount of the oxidant to give rise to a mixture of the trihydroxy lactone mixture (**3**) and the ene lactone mixture (**6**) besides the starting material. When the AD-mix was increased to two equivalents, only the trihydroxy lactone mixture (**3**) was obtained in 89% yield. Unfortunately, it was found that both of the diastereomeric mixtures (**3**) and (**6**) were inseparable even on a tlc plate. Moreover, the former lactone mixture (**3**) was stable under both acidic (*p*-TsOH) and basic (K_2CO_3) conditions preventing its equilibrium diastereomeric interconversion (**Scheme 2**).



Scheme 2

We, therefore, examined the transformation of these diastereomeric mixtures into a Sceletium alkaloid mesembrine (**4**) in order to determine the stereochemistry and the optical purities as well as to device an alternative enantiocontrolled route to the alkaloid. First, the trihydroxy lactone mixture (**3**) was treated with a little excess of lead tetraacetate in benzene to give the aldehyde (**7**) which without purification was reductively condensed with *N*-methylbenzylamine to give the tertiary amine (**8**) in a satisfactory yield. The amine (**8**) was then hydrogenated in the presence of di-*tert*-butoxycarbonic anhydride to yield the urethane (**9**) excellently by concurrent debenzylation and carbamoylation. On the other hand, the ene lactone mixture (**6**) was subjected to ozonolysis to give the same aldehyde (**7**) which was transformed into the same urethane (**9**) in a comparable good overall yield under the same conditions.

Having obtained the same urethane (**9**) from the two kinds of the product mixtures, we next examined its transformation into optically active mesembrine (**4**). Although it was not easy to remove the unnecessary oxygen functionality, we overcame by discovery of an unprecedented radical-initiated reductive cleavage. Thus, we first converted **9** into the keto hemithioacetal (**12**) in three steps *via* the lactol (**10**) and the hemithioketal (**11**) on sequential reduction, thiohemiketalization, and oxidation. Upon treatment with tri-*n*-butylstannane in refluxing benzene in the presence of AIBN, **11** furnished the desired keto aldehyde[8] (**15**) which was immediately treated with potassium hydroxide to give the cyclohexenone (**16**) in a satisfactory overall yield. The observed reductive cleavage reaction may be initiated by generation of the five-membered



Scheme 3

Reagents and conditions: i) $Pb(OAc)_4$, benzene, room temperature; then BnNHMe, $NaBH_3CN$, MS 4A, MeOH, room temperature (76%). ii) O_3, CH_2Cl_2, –78 °C, then Me_2S: then BnNHMe, $NaBH_3CN$, MS 4A, MeOH, room temperature (73%). iii) H_2, $Pd(OH)_2$ (cat.), $(Boc)_2O$, AcOEt-EtOH (~93%). iv) DIBAL, CH_2Cl_2, –78 °C. v) PhSH, $BF_3{\cdot}OEt_2$ (cat.), CH_2Cl_2, –78 °C ~ room temperature (54% from **8**). vi) Swern oxidation (~100%). vii) *n*-Bu_3SnH (6 equiv.), AIBN (cat.), benzene, reflux. viii) 10% KOH-MeOH (1:2), room temperature (~77% from **11**). ix) HCl-EtOH, reflux (~87%).

radical intermediate (**13**) which in turn was collapsed to the keto aldehyde (**15**) *via* the enolate radical (**14**). Finally, the cyclohexenone (**16**) was exposed to diluted hydrochloric acid to give optically active mesembrine[10] (**4**) in an excellent yield by concurrent removal of the carbamate group and intramolecular Michael addition. These transformations revealed the trihydroxy lactone mixture (**3**) to be (*R*)-**3** enriched by producing natural (–)-mesembrine[10] (**4**) in 50% ee[11] (from **3** generated by one equivalent of AD-mix-β) and 35% ee[11] (from **3** generated by two equivalents of AD-mix-β), respectively. While unnatural (+)-mesembrine (**4**) was obtained in 19% ee[11] from the ene lactone mixture (**6**) indicating it to be (*S*)-**6** enriched (**Scheme 3**).

Formation of (–)-mesembrine (**4**) from the trihydroxy-lactone mixture (**3**) may be reasoned in terms of the diastereoselective cyclization of the tetraol intermediate (**2**) in the most favorable conformation as we initially expected though some took an alternative pathway *via* the (*R*)-ene lactone (**6**). The formation of (+)-mesembrine (**4**) from the by-product ene lactone mixture (**6**) was presumed to be due to the rate difference of the dioxylation between the pro-*R* olefin and the pro-*S* olefin of the diene (**1**). Namely, the dioxylation of the pro-*S* olefin occurred a little faster to the pro-*R* counterpart to give the (*S*)-enriched diol (**5**) which then was transformed into the common tetraol (**2**) by the second dihydroxylation. When the oxidant was insufficient for the second reaction, the remaining (*S*)-enriched diol (**5**) was cyclized spontaneously under the conditions to give the (*S*)-enriched ene lactone mixture (**6**) as observed as shown in **Scheme 2**.

In conclusion, we have first time demonstrated the asymmetrization of a σ-symmetric substrate using an AD-mix reagent though in a moderate chiral induction rate and developed an alternative synthetic route to natural (–)-mesembrine (**4**) by discovery of the unprecedented radical-initiated reductive cleavage reaction.

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3. Our previous attemption based on conceptionally the same methodology employing the enantiospecific iodo-lactonization reaction, see: S. Takano, C. Murakata, Y. Imamura, N. Tamura, and K. Ogasawara, *Heterocycles*, 1981, **16**, 1291; S. Takano, C. Kasahara, and K. Ogasawara, *ibid.*, 1982, **19**, 1443.
4. A pertinent review of the Sceletium and the related alkaloids: J. R. Lewis, *Nat. Prod. Rept.*, 1994, **11**, 329 and the preceding reviews.
5. S. Takano, Y. Imamura, and K. Ogasawara, *Chem. Lett.*, 1981, 1385.
6. For brevity the stereochemistry of the quaternary center was indicated.
7. Purchased from Aldrich and used without further purification.
8. Among tested using **12** (OMe in place of SPh) as the substrate, only zinc in ethanol in the presence of hydrochloric acid afforded the desired product in only 8% yield. The other reagents including SmI_2-HMPA in THF-MeOH, Li in liq. NH_3, $CrCl_2$ in aqueous acetone, NaTeH in DMF, Mg in MeOH, Na(Hg) in THF-MeOH, and Zn-Cu and NH_4Cl in aqueous EtOH gave no trace of **15**.
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11. Optical purity was determined at the enone (**16**) by hplc using a chiral column (CHIRALCEL OD: eluent 15% *i*-PrOH-hexane).

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