THE REACTION OF 4,5-EPOXY-2(*E*)-HEXENOATE AND SECONDARY AMINES, TOTAL SYNTHESIS OF (-)-OSMUNDALACTONE AND (-)-FOROSAMINE

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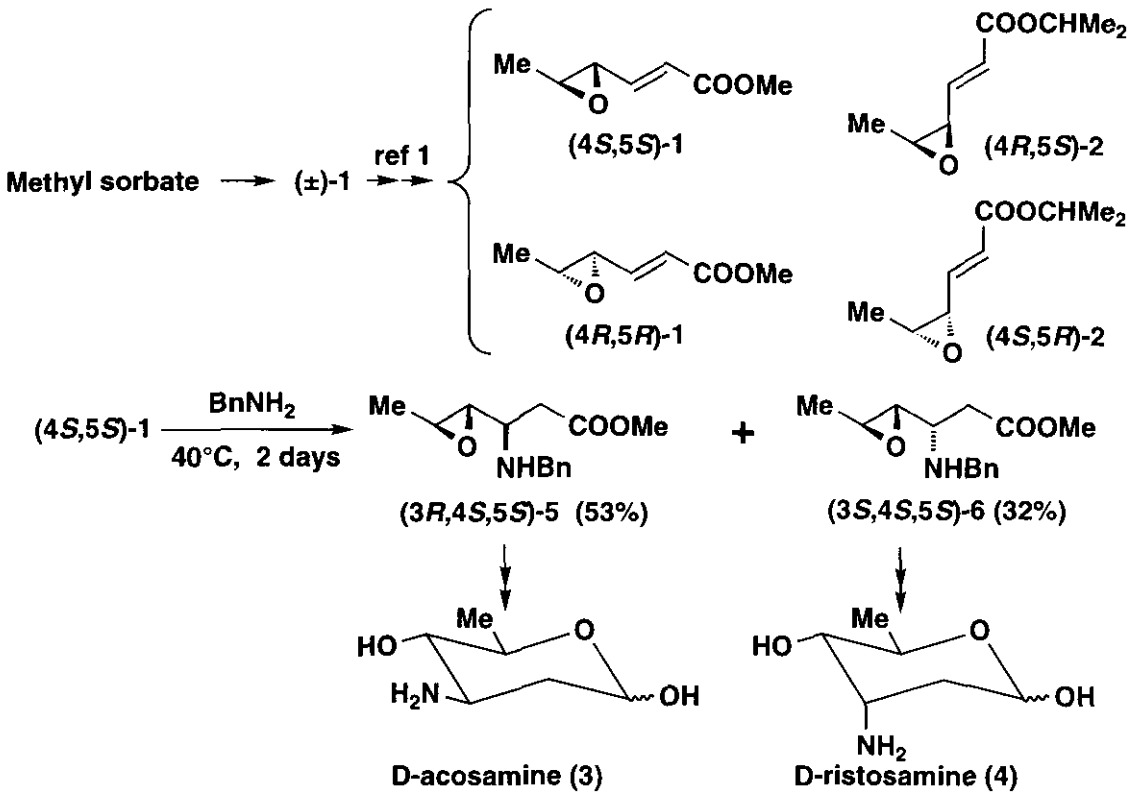
Abstract -A reaction of methy (4*R*,5*R*)-4,5-epoxy-2(*E*)-hexenoate (**1**) with *N*-methylbenzylamine gave a diastereomerically pure (3*S*,4*R*,5*R*)-**7** and (4*S*,5*R*)-**8**. The former was chemoenzymatically converted to (-)-osmundalactone (**12**) which is an aglycone of osmundalin. On the other hand, direct conjugated addition of dimethylamine to methyl (4*S*,5*S*)-4,5-epoxy-2(*E*)-hexenoate (**1**) followed by treatment with MeOH at 40°C exclusively provided (4*R*,5*S*)-**17** which was converted into L-forosamine (**19**).

In the proceeding paper, we reported syntheses of the each optically pure stereoisomer of 4,5-epoxy-2(*E*)-hexenoates (4*S*,5*S*)-**1**, (4*R*,5*R*)-**1**, (4*R*,5*S*)-**2** and (4*S*,5*R*)-**2** based on a chemoenzymatic method from an achiral precursor, methyl sorbate.[1] As a part of useful application of (4*S*,5*S*)-**1** to the syntheses of amino sugar or the related compounds, formal total syntheses of D-acosamine (**3**) and D-ristosamine (**4**) from (4*S*,5*S*)-**1** were acheieved.[2] The reaction of (4*S*,5*S*)-**1** with 4 equivalents of benzylamine was carried out to give the 1,4-addition products, (3*R*,4*S*,5*S*)-**5** (53%) and (3*S*,4*S*,5*S*)-**6** (32%). The intramolecular nucleophilic attack by ester carbonyl group upon epoxy ring of substrates, (3*R*,4*S*,5*S*)-**5** and (3*S*,4*S*,5*S*)-**6** results in the formal total syntheses of D-acosamine (**3**) and D-ristosamine (**4**), respectively.[2]

In the course of our continuing interest in the reaction of 4,5-epoxy-2(*E*)-hexenoates (4*S*,5*S*)-**1** with amine, the reaction of (4*S*,5*S*)-**1** with secondary amine aroused our interest. The reaction of (±)-**1** with 2 equivalents of *N*-methylbenzylamine at 40°C for 4 days gave a diastereomerically pure (±)-**7**[3] (68%) and (±)-**8**[4] (22%), while this reaction in the presence of MeOH provided (±)-**7** (30%) and (±)-**8** (66%). In case of the latter, solvent effect appeared and product ratio of (±)-**7** and (±)-**8** was reversed. In order to determine the structure of (±)-**7**, possible two authentic samples were prepared. The reaction of (±)-(3,4)-*syn* **5** and (±)-(3,4)-*anti* **6** with an excess of methyl iodide at 0°C provided the *N*-methylated amines, (±)-(3,4)-*syn* **7** (48%) and (±)-(3,4)-*anti* **9** (33%), respectively. Physical data of the present (±)-**7** were identical with those of authentic (±)-(3,4)-*syn* **7**. For the purpose of determining the structure of (±)-**8**, compound (±)-**8** was converted into the acetate (±)-**10** (88%) and the acetal (±)-**11** (47%) by applying



Scheme 1

Evans method.[5] Chemical shift due to C_5-H of (±)-**10** was appeared in the lower field (δ 5.21, dq, J=6, 9 Hz) in comparison with that (δ 4.11, quintet, J=6 Hz) of (±)-**8** and thence the hydroxyl group was located at C_5-position. The *anti*-stereochemistry of (±)-**8** was confirmed by the following fact. NOE experiments of (±)-**11** were shown in Figure 1 and the coupling constants of the C_3-axial and C_4-axial protons, and the C_4-axial and C_5-axial protons were 10 Hz and 10 Hz, respectively, clearly indicating the starting (±)-**8** possessed the *anti*-configuration. Then, the formation of the diastereomerically pure (±)-**7** and (4,5)-*anti* **8** was explained by the following experiments. When a solution of (±)-**7** in MeOH was allowed to stand at 40°C for a long time (4 days), the rearranged (±)-**8** was obtained in 54% yield along with the starting (±)-**7** (30%). The same reaction was carried out for a short time (2 days), (±)-**8** (43%) and the intermediary (±)-**1** (16%) were obtained along with the starting (±)-**7** (21%). A solution of (±)-**8** in MeOH was exposed at 40°C for 4 days, no change of (±)-**8** was observed. Based on the inspection of the stability of (±)-**7** and (±)-**9** by using Dreiding Stereomodels, (±)-**9** was presumably more unstable than (±)-**7**. Because, in case of (±)-**9**, steric repulsion by between C_5-methyl group and C_3-substituents appeared to be larger than that of (±)-**7**. Consequently, the rate of conversion of the unstable (±)-**9** into (±)-**1** is presumably faster than that of conversion of (±)-**7** into (±)-**1**. Actually, an exposure of (±)-**9** in MeOH at 40°C for 4 days gave exclusively (±)-**8** in 83% yield. According to the above mentioned conversion experiments, the intermediary products on exposure of (±)-**7** in MeOH for 2 days and (±)-**9** in

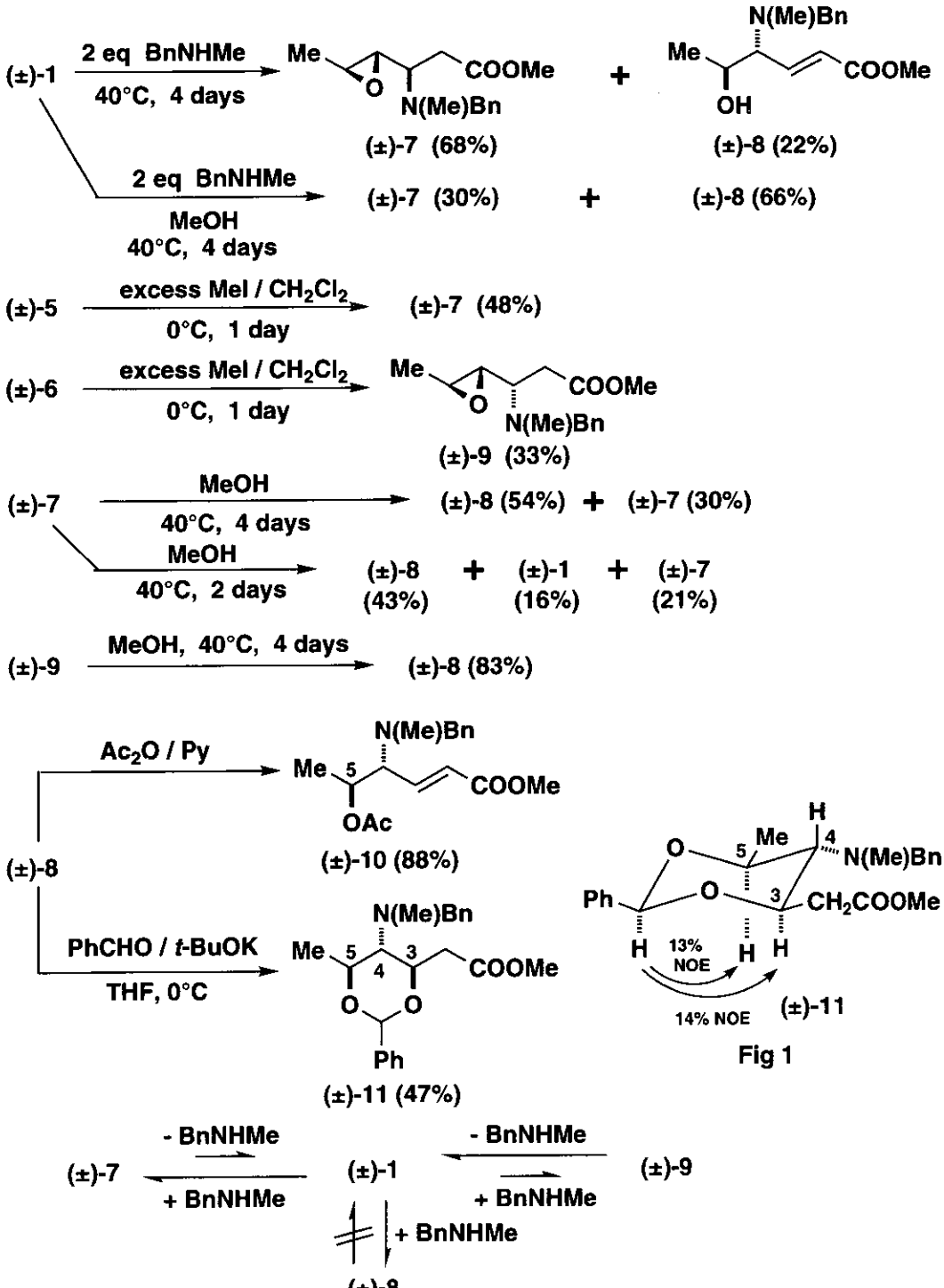
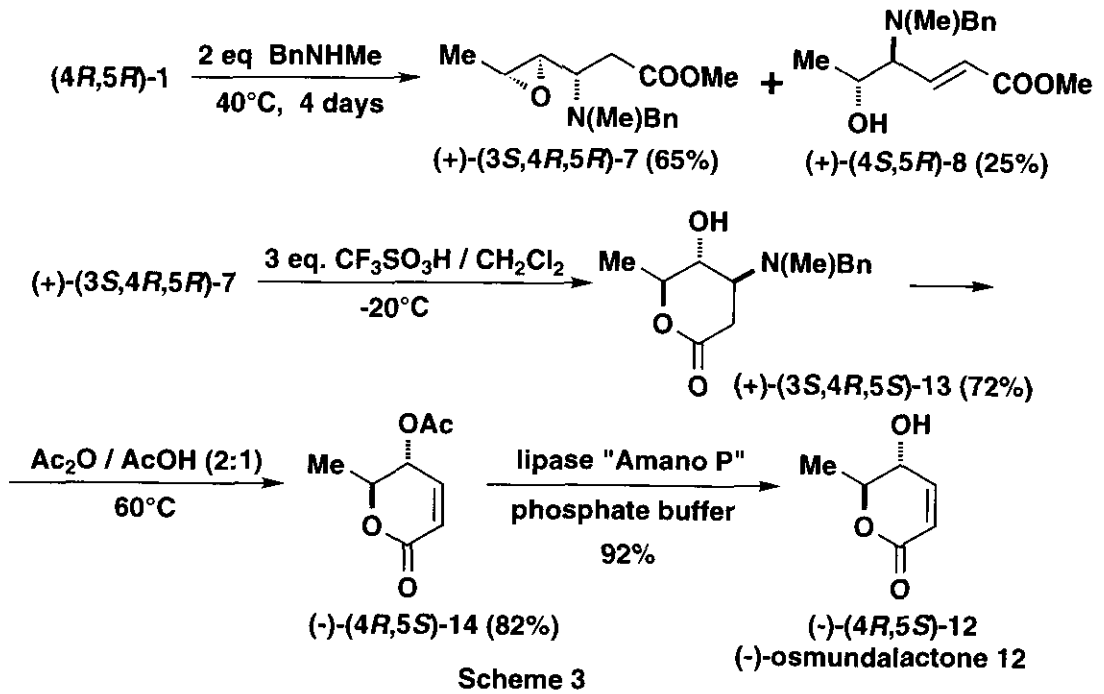


Fig 1

Scheme 2

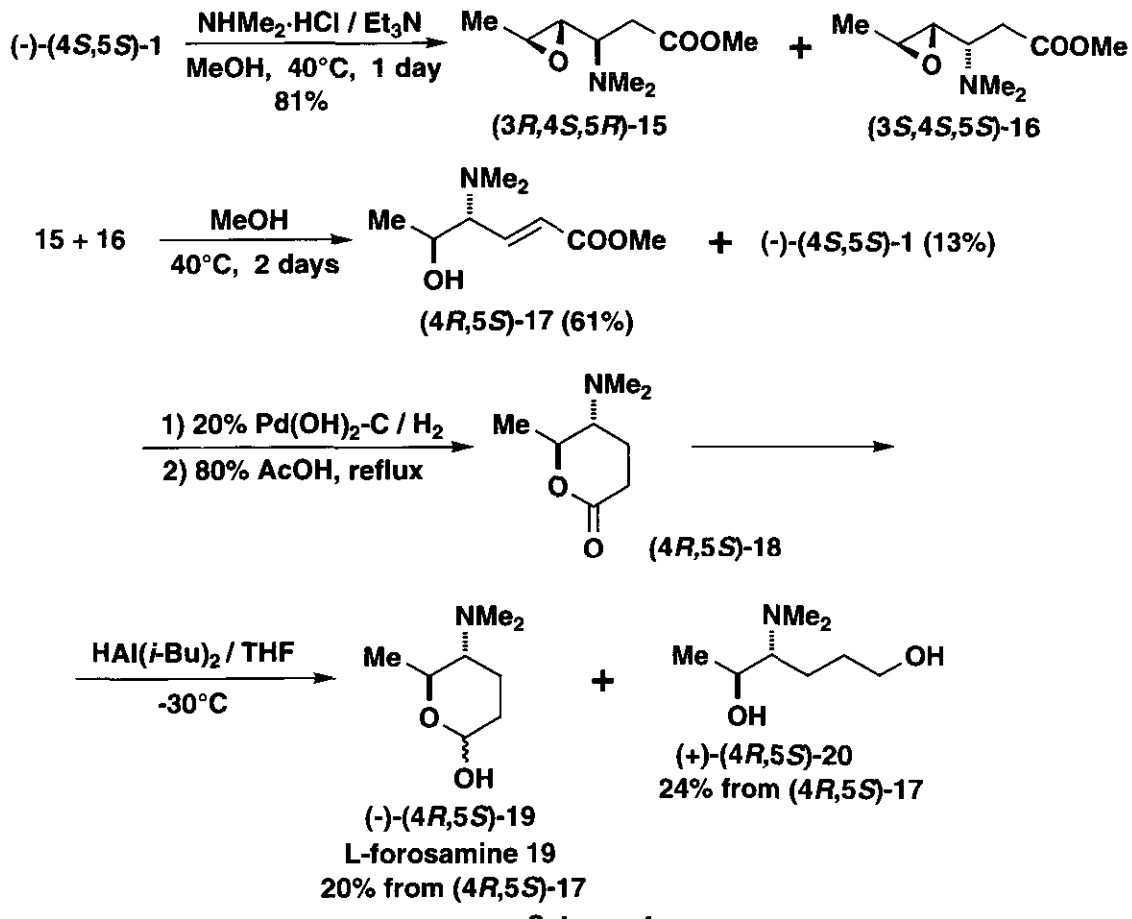
MeOH for 4 days are the retro-Michael reaction product, 4,5-epoxy-2(*E*)-hexenoate ((±)-**1**). From these experimental evidences, the epoxy ester ((±)-**1**) is generated from (±)-**7** or/and (±)-**9** and the liberated *N*-methylbenzylamine again attacks at C_4-position of (±)-**1** in the manner of *anti*-stereochemistry to afford the (4,5)-*anti* **8** corresponding to the thermodynamic controlled product. On the whole, the reaction of (±)-**1** with *N*-methylbenzylamine is explained as follows: At first, competitive attack by the nucleophile at C_3- and C_4-positions of (±)-**1** presumably occurs to afford (±)-**7**, (±)-**9** and the (4,5)-*anti* **8**. Then more unstable (±)-**9** could be converted into (±)-**8** and partial conversion of (±)-**7** into (±)-**8** is probably occurred. Finally, the reaction of (±)-**1** with *N*-methylbenzylamine gave the (3,4)-*syn* **7** corresponding to the kinetic controlled product and the (4,5)-*anti* **8** corresponding to the thermodynamic controlled product. The difference of product ratio of (±)-**7** and (±)-**8** between absence of MeOH and presence of MeOH is explained by the solvent effect. Methanol presumably accelerates the rate of the retro-Michael process to afford (±)-**1** and then the thermodynamic (±)-**8** could be obtained from (±)-**1** as a major product.



Scheme 3

This reaction was effectively applied for the synthesis of osmundalactone (**12**) which is an aglycone of osmundalin isolated from *Osmunda japonica* Thunberg (Akaboshi zenmai), exhibiting a feeding inhibitor for the larvae of butterfly *Eurema hecabe mandrarina*.[6a,b] The reaction of (+)-(4*R*,5*R*)-**1** with *N*-methylbenzylamine gave (+)-(3*S*,4*R*,5*R*)-**7** (65%, $[\alpha]_D$ +17.3° (c=0.98, $CHCl_3$)) and (+)-(4*S*,5*R*)-**8** (25%, $[\alpha]_D$ +52.2° (c=1.01, $CHCl_3$)). Treatment of (+)-**7** with trifluoromethanesulfonic acid (CF_3SO_3H) provided exclusively δ-lactone ((+)-(3*S*,4*R*,5*S*)-**13**) (72% $[\alpha]_D$ +53.2° (c=0.76, $CHCl_3$)) which was subjected to acetylation[7] with Ac_2O-AcOH (2:1) to afford an acetate (-)-(4*R*,5*S*)-**14** (82%, $[\alpha]_D$ −169.8° (c=0.73, $CHCl_3$)) with an elimination of *N*-methylbenzylamine. In this case, the liberated *N*-

methylbenzylamine was acetylated in 98% yield and did not work as a nucleophilic reagent against the 2*H*-pyran-2-one moiety of the generated substrate (-)-**14**. The physical data ($[\alpha]_D$ and NMR) of (-)-**14** were identical with those ($[\alpha]_D$ –172° (c=2.8, $CHCl_3$) and NMR) of the reported (-)-**14**.[6a] Finally, the acetate ((-)-**14**) was exposed to the enzymatic hydrolysis using the lipase "Amano P" from *Pseudomonas* sp. and converted to the hydroxy δ-lactone ((-)-(4*R*,5*S*)-**12**) (92%, $[\alpha]_D$ –69.0° (c=0.46, H_2O)) whose physical data ($[\alpha]_D$ and NMR) were identical with those ($[\alpha]_D$ –70.6° (c=2.0, H_2O)) of the natural (-)-osmundalactone (**12**).[6a]



Scheme 4

Then the reaction of (-)-(4*S*,5*S*)-**1** with dimethylamine was carried out. The reaction of (-)-(4*S*,5*S*)-**1** with dimethylamine hydrochloride (2 equivalents)-triethylamine (2 equivalents) in MeOH gave a 1.7 : 1 diastereomeric mixture of (3*R*,4*S*,5*R*)-**15** and (3*S*,4*S*,5*S*)-**16** in 81% yield. This mixture was again exposed in MeOH at 40°C for 2 days provided the rearranged (-)-(4*R*,5*S*)-**17** (61%, $[\alpha]_D$ –115.9° (c=1.02, $CHCl_3$)) and (4*S*,5*S*)-**1** (13%) along with the starting mixture (25% recovery) of **15** and **16**. In the first place, the retro-Michael reaction in the mixture of **15** and **16** occurred to give the elimination product 4,5-epoxy-2(*E*)-hexenoate (**1**) and the generated dimethylamine again attacked at C_4-position of (4*S*,5*S*)-**1** in

the manner of *anti*-stereochemistry to afford the (4,5)-*anti* **17**. Hydrogenation of (-)-(4*R*,5*S*)-**17** followed by treatment with 80% AcOH gave the δ-lactone ((4*R*,5*S*)-**18**) which was reduced with diisobutylaluminum hydride (DIBAH) to provide an amino sugar (-)-(4*R*,5*S*)-**19** (20% from (-)-**17**, $[\alpha]_D$ –85.7° (c=0.78, MeOH)) and a diol (+)-(4*R*,5*S*)-**20** (24% from (-)-**17**, $[\alpha]_D$ +10.7° (c=0.93, MeOH)). The physical data of the synthesized (-)-**19** were consistent with those ($[\alpha]_D$ +86.1° (c=0.9, MeOH) and NMR) of D-forosamine **19**.[8]

In conclusion, in the reaction of 4,5-epoxy-2(*E*)-hexenoate (**1**) with secondary amine, 1,4-conjugated addition of secondary amine to the α,β-unsaturated ester moiety may occur at first to provide a diastereomeric mixture of (4,5)-epoxy-3-*N*-substituted amino esters. From this mixture, the product distribution between 4,5-*anti*-2(*E*)-hexenoate such as **8** or **17** and the enantiomerically pure 4,5-epoxy-3-*N*-substituted amino ester such as **7** was found to be depended upon the reaction condition and the nature of the used secondary amine.

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2. M. Ono, C. Saotome, and H. Akita, *Heterocycles*, 1997, **45**, 1257.
3. Satisfactory analytical data were obtained for all new compounds.
4. (±)-**8**; ^{1}H-NMR($CDCl_3$) δ 1.20 (3H, d, J=6 Hz, C_5-Me), 2.22 (3H, s, NMe), 2.88 (1H, dd, J=6, 10 Hz, C_4-H), 3.49, 3.67 (each 1H, d, J=13 Hz, NCH_2Ph), 3.77 (3H, s, COOMe), 4.11 (1H, quintet, J=6, 6 Hz, C_5-H), 5.98 (1H, d, J=16 Hz, C_2-H), 7.01 (1H, dd, J=10, 16 Hz, C_3-H), 7.23-7.34 (5H, m, aromatic-H). IR (neat); 3439, 1723 cm^{-1}. FAB-MS (*m/z*); 264 (M^++1).
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7. As a preliminary experiment, acetylation of (±)-**13** with Ac_2O-pyridine gave the corresponding acetate (95%) which was treated with Ac_2O/AcOH (2:1) to afford (±)-**14** (87%) and *N*-methylbenzylamine acetate (68%).
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