

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

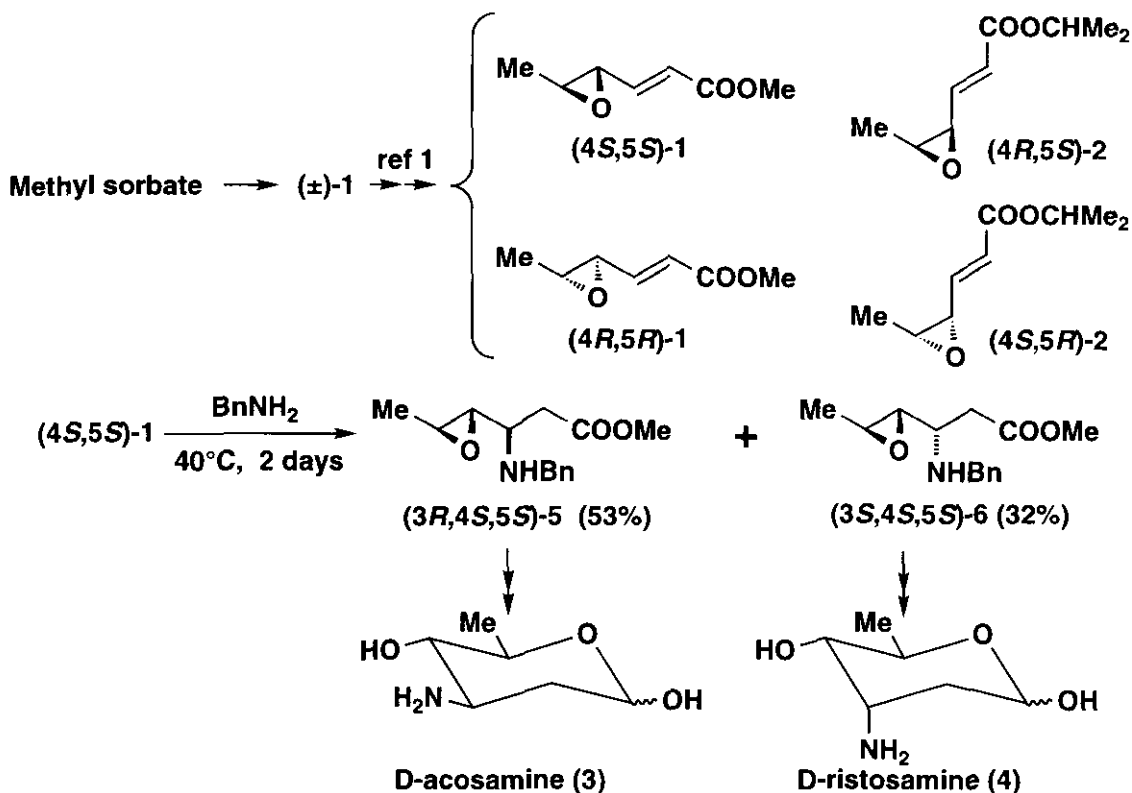
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Abstract -A reaction of methyl (4*R*,5*R*)-4,5-epoxy-2(*E*)-hexenoate (**1**) with *N*-methylbenzylamine gave a diastereomerically pure (3*S*,4*R*,5*R*)-**7** and (4*S*,5*R*)-**8**. The former was chemoenzymatically converted to (-)-osmundalactone (**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**).

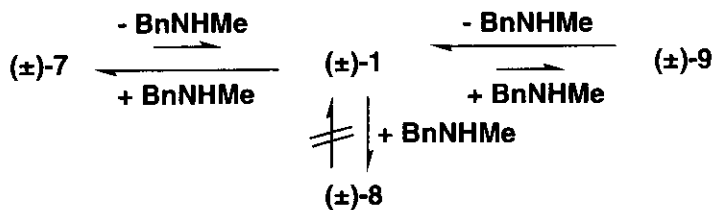
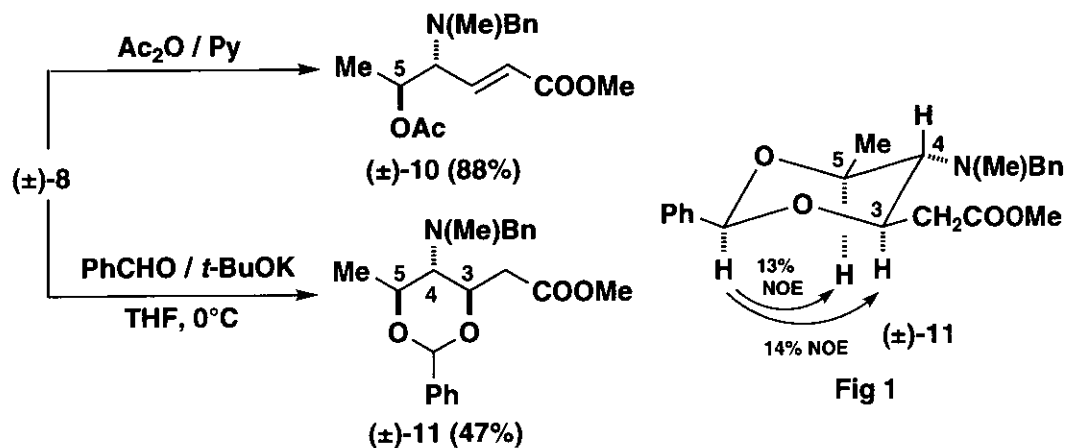
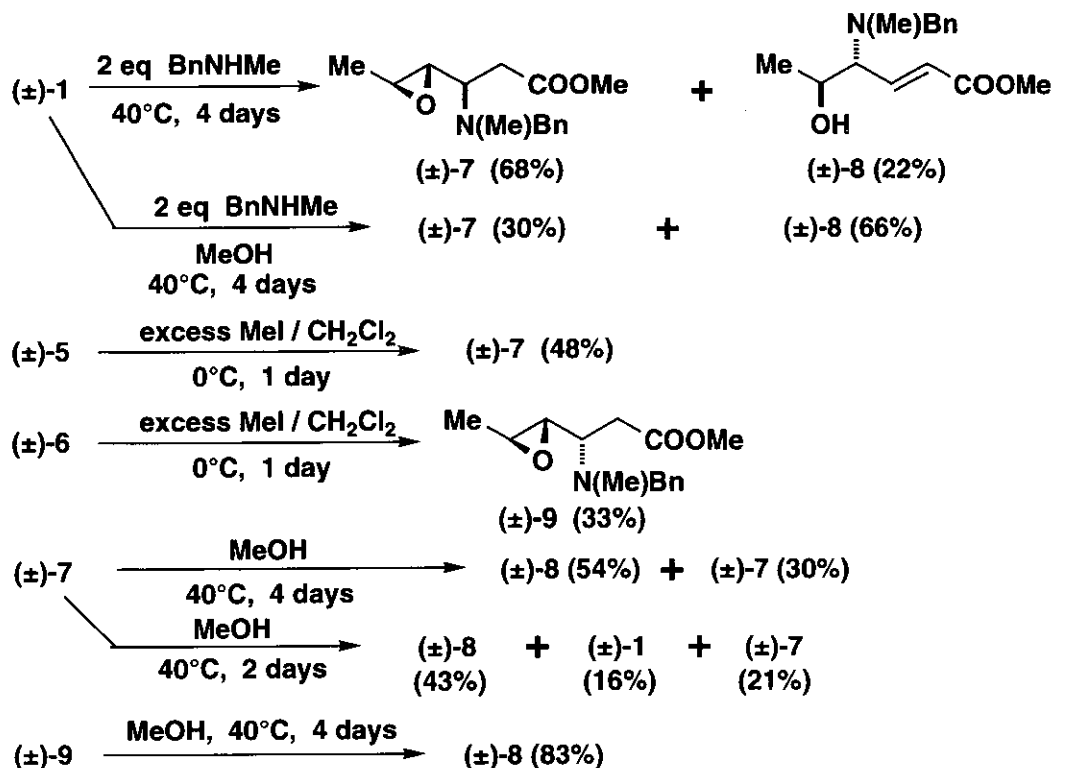
In the preceding paper, we reported syntheses of the each optically pure stereoisomer of 4,5-epoxy-2(*E*)-hexenoates (4*S*,5*S*)-**1**, (4*R*,5*R*)-**1**, (4*R*,5*S*)-**2** and (4*S*,5*R*)-**2** based on a chemoenzymatic method from an achiral precursor, methyl sorbate.¹ As a part of useful application 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 achieved.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



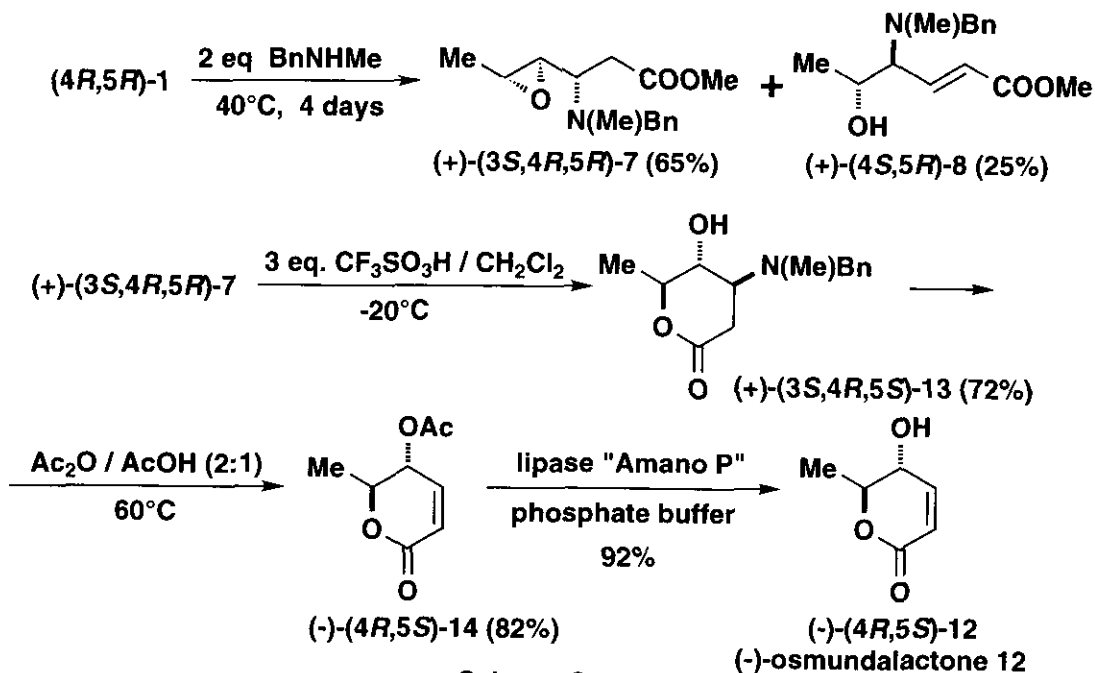
Scheme 1

Evans method.⁵ Chemical shift due to C₅-H of (\pm)-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 (\pm)-8 and thence the hydroxyl group was located at C₅-position. The *anti*-stereochemistry of (\pm)-8 was confirmed by the following fact. NOE experiments of (\pm)-11 were shown in Figure 1 and the coupling constants of the C₃-axial and C₄-axial protons, and the C₄-axial and C₅-axial protons were 10 Hz and 10 Hz, respectively, clearly indicating the starting (\pm)-8 possessed the *anti*-configuration. Then, the formation of the diastereomerically pure (\pm)-7 and (4,5)-*anti* 8 was explained by the following experiments. When a solution of (\pm)-7 in MeOH was allowed to stand at 40°C for a long time (4 days), the rearranged (\pm)-8 was obtained in 54% yield along with the starting (\pm)-7 (30%). The same reaction was carried out for a short time (2 days), (\pm)-8 (43%) and the intermediary (\pm)-1 (16%) were obtained along with the starting (\pm)-7 (21%). A solution of (\pm)-8 in MeOH was exposed at 40°C for 4 days, no change of (\pm)-8 was observed. Based on the inspection of the stability of (\pm)-7 and (\pm)-9 by using Dreiding Stereomodels, (\pm)-9 was presumably more unstable than (\pm)-7. Because, in case of (\pm)-9, steric repulsion by between C₅-methyl group and C₃-substituents appeared to be larger than that of (\pm)-7. Consequently, the rate of conversion of the unstable (\pm)-9 into (\pm)-1 is presumably faster than that of conversion of (\pm)-7 into (\pm)-1. Actually, an exposure of (\pm)-9 in MeOH at 40°C for 4 days gave exclusively (\pm)-8 in 83% yield. According to the above mentioned conversion experiments, the intermediary products on exposure of (\pm)-7 in MeOH for 2 days and (\pm)-9 in



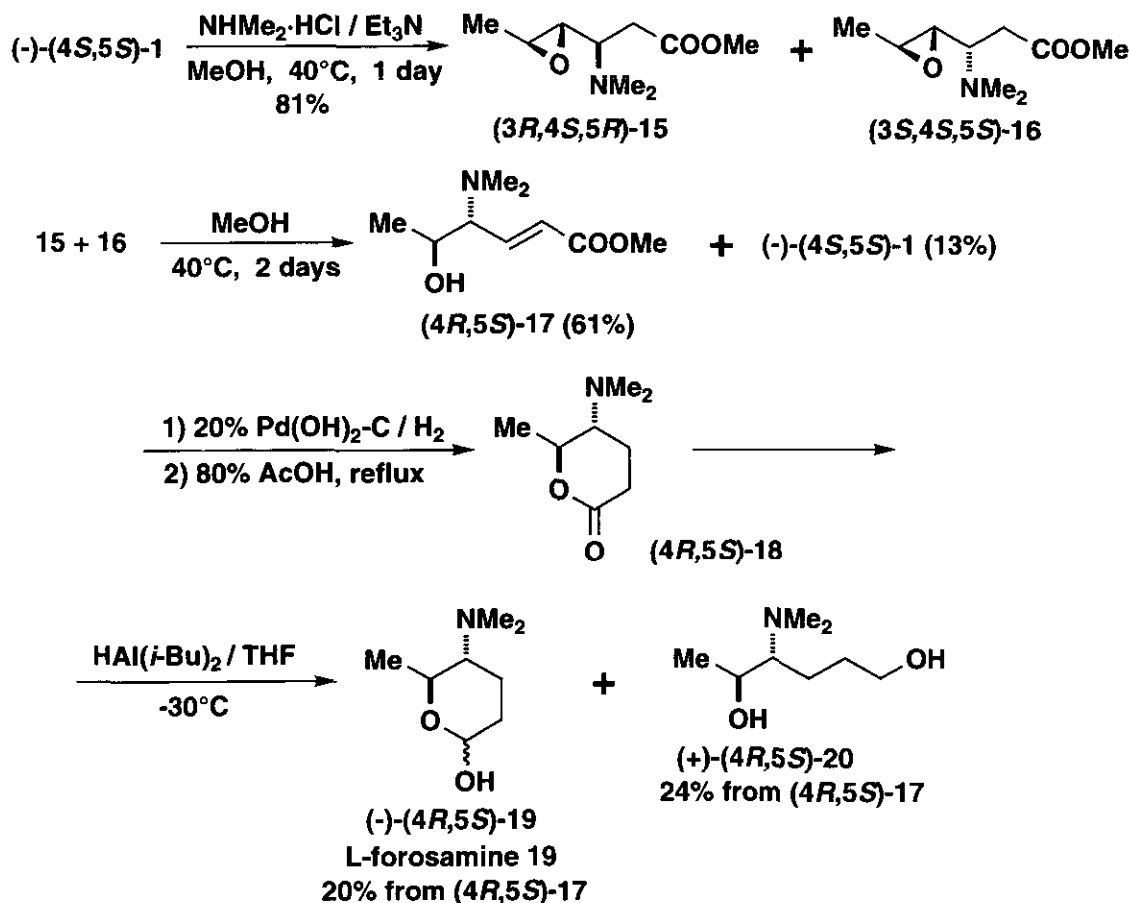
Scheme 2

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 C₄-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 C₃- and C₄-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.



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 mandarina*.^{6a,b} The reaction of (+)-(4*R*,5*R*)-**1** with *N*-methylbenzylamine gave (+)-(3*S*,4*R*,5*R*)-**7** (65%, [α]_D +17.3° (c=0.98, CHCl₃)) and (+)-(4*S*,5*R*)-**8** (25%, [α]_D +52.2° (c=1.01, CHCl₃)). Treatment of (+)-**7** with trifluoromethanesulfonic acid (CF₃SO₃H) provided exclusively δ -lactone ((+)-(3*S*,4*R*,5*S*)-**13**) (72% [α]_D +53.2° (c=0.76, CHCl₃)) which was subjected to acetylation⁷ with Ac₂O-AcOH (2:1) to afford an acetate (-)-(4*R*,5*S*)-**14** (82%, [α]_D -169.8° (c=0.73, CHCl₃)) 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 ($[\alpha]_D -172^\circ$ ($c=2.8$, 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%, $[\alpha]_D -69.0^\circ$ ($c=0.46$, H_2O)) whose physical data ($[\alpha]_D$ and NMR) were identical with those ($[\alpha]_D -70.6^\circ$ ($c=2.0$, 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%, $[\alpha]_D -115.9^\circ$ ($c=1.02$, 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**, $[\alpha]_D -85.7^\circ$ ($c=0.78$, MeOH)) and a diol (+)-(4*R*,5*S*)-**20** (24% from (-)-**17**, $[\alpha]_D +10.7^\circ$ ($c=0.93$, MeOH)). The physical data of the synthesized (-)-**19** were consistent with those ($[\alpha]_D +86.1^\circ$ ($c=0.9$, MeOH) and NMR) of D-fofosamine **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. (\pm)-**8**; ¹H-NMR(CDCl₃) δ 1.20 (3H, d, $J=6$ Hz, C₅-Me), 2.22 (3H, s, NMe), 2.88 (1H, dd, $J=6, 10$ Hz, C₄-H), 3.49, 3.67 (each 1H, d, $J=13$ Hz, NCH₂Ph), 3.77 (3H, s, COOMe), 4.11 (1H, quintet, $J=6, 6$ Hz, C₅-H), 5.98 (1H, d, $J=16$ Hz, C₂-H), 7.01 (1H, dd, $J=10, 16$ Hz, C₃-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 (\pm)-**13** with Ac₂O-pyridine gave the corresponding acetate (95%) which was treated with Ac₂O/AcOH (2:1) to afford (\pm)-**14** (87%) and *N*-methylbenzylamine acetate (68%).
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