Pergamon

*Tetrahedron: Asymmetry*, Vol. 8, No. 15, pp. 2519–2521, 1997

Printed in Great Britain
PII: S0957-4166(97)00299-1
0957-4166/97 $17.00 + 0.00

# A new enantiocontrolled synthesis of (−)-(*R*)-mevalonolactone

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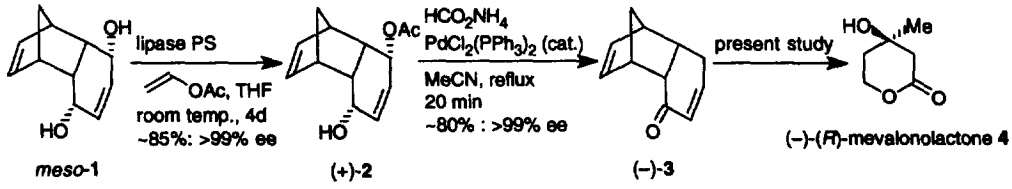
***Abstract:*** A new procedure leading to enantiomerically pure (−)-(*R*)-mevalonolactone has been devised *via* a β-methylation of the α,β-enone functionality of a chiral equivalent of cyclohexa-2,5-dienone. © 1997 Elsevier Science Ltd

We have found that the tricyclic *meso*-ene-1,4-diol **1** is enantiospecifically desymmetrized in an organic solvent containing vinyl acetate in the presence of a lipase to give the enantiomerically pure (+)-monoacetate[1] **2**. Moreover, we have found that the enantiomerically pure acetate **2** thus obtained furnished the α,β-unsaturated ketone (−)-**3** in one step without losing its original chiral integrity on reflux with ammonium formate in the presence of a catalytic amount of dichlorobis(triphenylphosphine)palladium(II).[1,2] These findings led us to use the enantiomerically pure enone **3** as a versatile chiral building block in particular as a chiral equivalent of cyclohexa-2,5-dienone as it allows not only strict control over the stereochemical course of operations on its enone periphery owing to its biased framework, but also facile thermal removal of a cyclopentadiene leaving an olefin functionality after an appropriate modification.[3,4] However, a difficulty we encountered in using **3** was the introduction of a quaternary stereogenic center at the β-carbon of the enone functionality which seriously restricted its versatile utilization. We therefore examined the β-functionalization of the enone system of **3** so as to obtain a β-substituted enone which is capable of constructing a quaternary stereogenic center at the β-carbon by stereoselective 1,4-addition from the convex face of the molecule. We report herein an enantiocontrolled synthesis of (−)-(*R*)-mevalonolactone[5] **4**, the lactone form of (−)-(*R*)-mevalonic acid and an important intermediate in biosynthetic pathways leading to sterols, terpenes, carotenoids, and other isoprenoids, as a simple example for the construction of the quaternary stereogenic center at the β-carbon of the enantiomerically pure enone (−)-**3** through installation of a methyl group on the β-carbon of the enone functionality (Scheme 1).




**Scheme 1.**

Employing the β-alkylation procedure for 2-cyclohexenone developed by Kozikowski and Jung,[6] we examined methylation at the β-carbon of the enone functionality of **3** though introduction of methyl group was not demonstrated in the original procedure. Thus, a mixture of the enantiomerically pure enone (−)-**3** (>99% ee) and a slight excess of triphenylphosphine (1.1 equiv.) in THF was treated with a slight excess of *tert*-butyldimethylsilyl triflate (1.1 equiv.) at −78°C for 30 min to form the allylphosphonium triflate **5**. The reaction mixture containing **5** was then exposed to butyllithium (1.2 equiv.) in the same flask at −78°C to generate the phosphonium ylide to which gaseous formaldehyde was introduced at the same temperature. The reaction occurred readily to furnish the desired β-methyl

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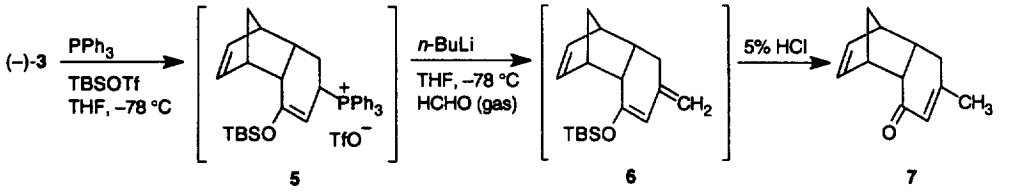
enone[7] **7**, $[\alpha]_D^{30}$ −280.5 (*c* 1.0, $CHCl_3$), in 78% yield after treatment of the reaction mixture containing the 1,3-diene intermediate **6** with 5% hydrochloric acid at −78°C to room temperature. Optical purity of the product was determined to be >99% ee by HPLC using a chiral column (CHIRALCEL OJ, elution with *i*-PrOH–hexane, 1:20) (Scheme 2).




Scheme 2.

In order to construct a quaternary stereogenic center at the β-carbon of the enone functionality, **7** was treated with 30% hydrogen peroxide (1.5 equiv.) in methanol in the presence of a catalytic amount of 0.5 N sodium hydroxide (0.1 equiv.). As expected, a stereoselective reaction took place from the convex face to give the *exo*-epoxide **8**, mp 71.5°C, $[\alpha]_D^{29}$ −12.5 (*c* 1.0, $CHCl_3$), as a single diastereomer in 88% yield. Regioselective cleavage of the epoxide **8** was efficiently achieved by use of aluminum amalgam[8] (15 equiv.) in isopropanol at room temperature to afford the β-ketol **9**, mp 85.2°C, $[\alpha]_D^{31}$ −223.8 (*c* 0.9, $CHCl_3$), in 98% yield. However, an alternative procedure using a phenylselenolate[5,9] did not afford **9**, cleanly, which was accompanied by a considerable amount of the enone **7** resulting from **9** by a β-elimination under the conditions. Reduction of the β-ketol **9** with diisobutylaluminum hydride in dichloromethane at −78°C, occurred stereoselctively from the convex face to afford the single 1,3-*trans*-diol **10**, mp 117.0°C, $[\alpha]_D^{28}$ +32.1 (*c* 1.0, $CHCl_3$), in 89% yield. On thermolysis in diphenyl ether at 270°C in the presence of sodium hydrogen carbonate,[10] **10** furnished the cyclohexenediol **11**, mp 98.7°C, $[\alpha]_D^{27}$ −47.9 (*c* 2.4, $CHCl_3$), in 82% yield after 30 min by retro-Diels-Alder reaction. Addition of sodium hydrogen carbonate in the reaction medium was desirable to prevent elimination of the tertiary hydroxy group. To obtain mevalonolactone **4**, the product **11** was ozonized in methanol at −78°C to cleave its double bond and the ozonide **12** generated was reduced immediately with sodium borohydride in the same flask to generate the triol **14**, which, without isolation, was treated with aqueous sodium periodate to give the hydroxy-aldehyde **14** by glycol cleavage. Finally, the product isolated as a lactol **15** was oxidized with Jones' reagent[5b] to afford (−)-(*R*)-mevalonolactone **4**, $[\alpha]_D^{30}$ −22.0 (*c* 0.4, EtOH) {lit.[5b]: $[\alpha]_D^{28}$ −21.8 (*c* 1.0, EtOH)}, in 40% overall yield from the cyclohexenediol **11** (Scheme 3).

In summary, a new enantiocontrolled route to (−)-(*R*)-mevalonolactone has been developed using a chiral equivalent of cyclohexa-2,5-dienone by stereoselective construction of the quaternary stereogenic center through a β-methylation of the α,β-enone functionality.

## Acknowledgements

We are grateful to the Japan Society for the Promotion of Science for Japanese Junior Scientists for a fellowship (to T. K.).

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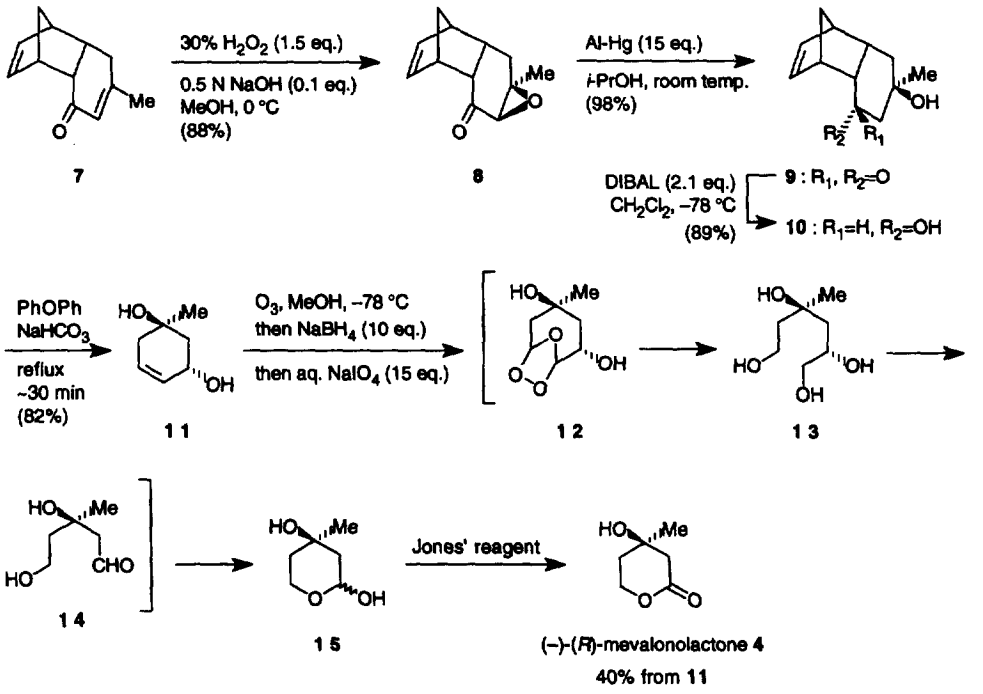


**Scheme 3.**


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*(Received in Japan 19 June 1997)*