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A SYNTHESIS OF (R)-(-)-MEVALONOLACTONE BY THE COMBINATION OF ENZYMATIC AND CHEMICAL METHODS†

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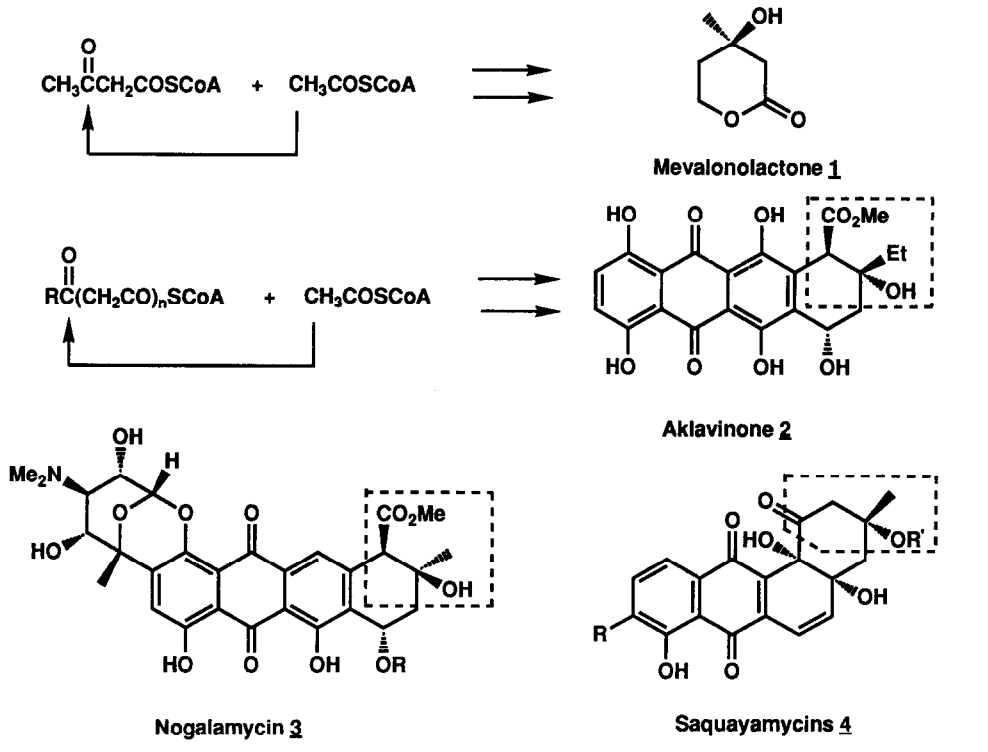
Abstract -- (R)-(-)-Mevalonolactone was synthesized starting from a chiral tertiary α-benzyloxy ester, obtained by the lipase-catalyzed enantioselective hydrolysis of the corresponding racemate, in 7 steps and 21.5% overall yield. *Intramolecular Friedel-Crafts reaction of an intermediate worked well as the* key-step for the new carbon-carbon bond formation.

(R)-(-)-Mevalonolactone (**1**) was first isolated as a growth factor of Lactobacillus homohiochii, L. heterohiochii,[1] and L. acidophilus,[2] which was later revealed to be the key intermediate in isoprenoid biosynthesis.[3] A number of chiral syntheses and fermentation production have been reported, because of its biological importance.[4,5] Furthermore, this compound is a challenging target for asymmetric synthesis, since it possesses a chiral tertiary β-hydroxy carbonyl moiety, which is also found in a number of anthraquinone antibiotics, for example, aklavinone (**2**),[6] nogalamycin (**3**),[7] saquayamycins (**4**)[8] and others.[9] Such a structural unit, the chiral tertiary hydroxy group, is biosynthetically derived from acetyl CoA via the condensation with acetoacetyl CoA or polyketide intermediate (Scheme 1).[10,11] For the chemical synthesis of this class of compounds, there must be developed the chiral starting material and synthetic route.

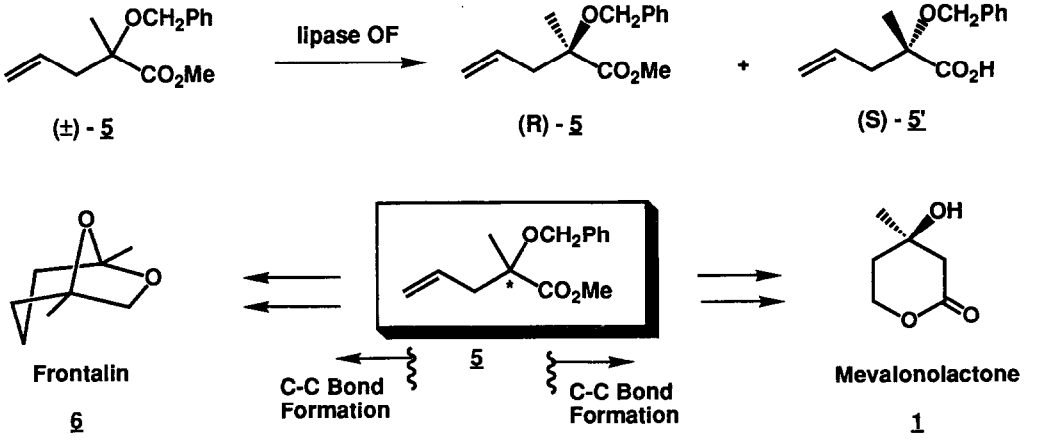
Recently we have reported an enzymatic preparation of a chiral tertiary α-benzyloxy ester **5** using commercially available lipase OF from Candida cylindracea (Scheme 2).[12] Both enantiomers of **5** have efficiently been obtained. Ester **5** will find broad synthetic utility as a chiral "citramalic acid equivalent", and which has been demonstrated in our chiral synthesis of (-)-frontalin (**6**) via carbon-chain elongation from the allylic terminal of **5**. In the present paper, we wish to describe another example which clearly shows the utility of **5**, by the chiral synthesis

†Preparation of Chiral Compound using Enzymes, Part 4. For part 3, see ref 12. The experimental part of this work was taken from forthcoming M. S. thesis of H. K. (March, 1991).

of (R)-(-)-mevalonolactone via carbon-chain elongation to the carboxylic ester direction of **5**.



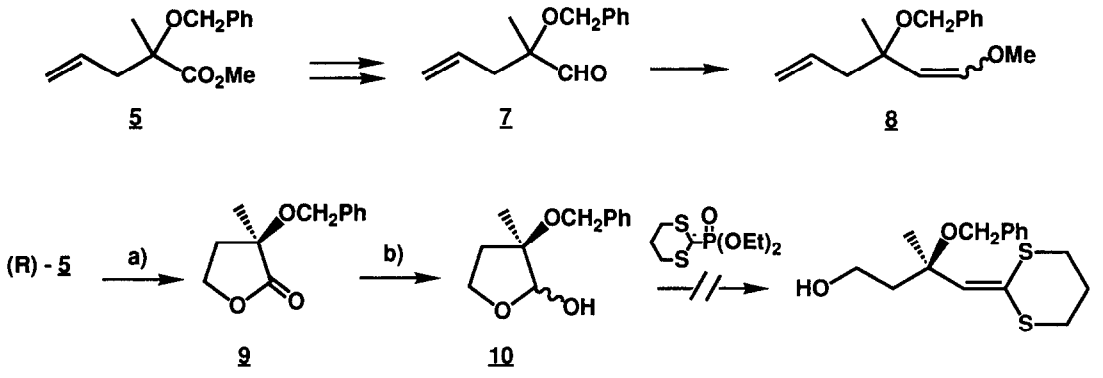
Scheme 1. Biosynthesis of Mevalonolactone and Anthraquinone Antibiotics



Scheme 2. Synthetic Plan

At the outset, the requisite C-C bond elongation was examined, which turned out to be highly troublesome because of the steric hindrance of the quarternary carbon, although an Arndt-Eistert approach using an analogous compound had been reported.[13] On the other hand, aldehyde **7** readily available from **5** was reacted with a Wittig reagent derived from methoxymethyltriphenylphosphonium bromide[14] to make successful in the formation of carbon-carbon double bond. However, all attempts to obtain β-benzyloxyaldehyde by the acidic cleavage of enol ether **8** resulted in the complex mixture, because it has an aptitude to generate a tertiary allylic carbocation.

Encouraged by the fact that C=C double bond formation worked well, we attempted a lactol (cyclic hemiacetal) opening reaction of **10**, which had been reported by Suzuki and co-workers as a potent method from lactol to one-carbon homologated lactone.[15] Ester (R)-5 [$[\alpha]_D^{25}$ +3.8° ($CHCl_3$), >99% e.e.][12] was ozonolyzed in methanol followed by reductive workup to give a lactone **9** in 86.2% yield. Diisobutylaluminum hydride reduction of **9** yielded a diastereomeric mixture of lactol **10** in 84.8% yield. The next attempted chain-elongation step, however, resulted in the recovery of starting material or a complex mixture of the products under various conditions (Scheme 3).

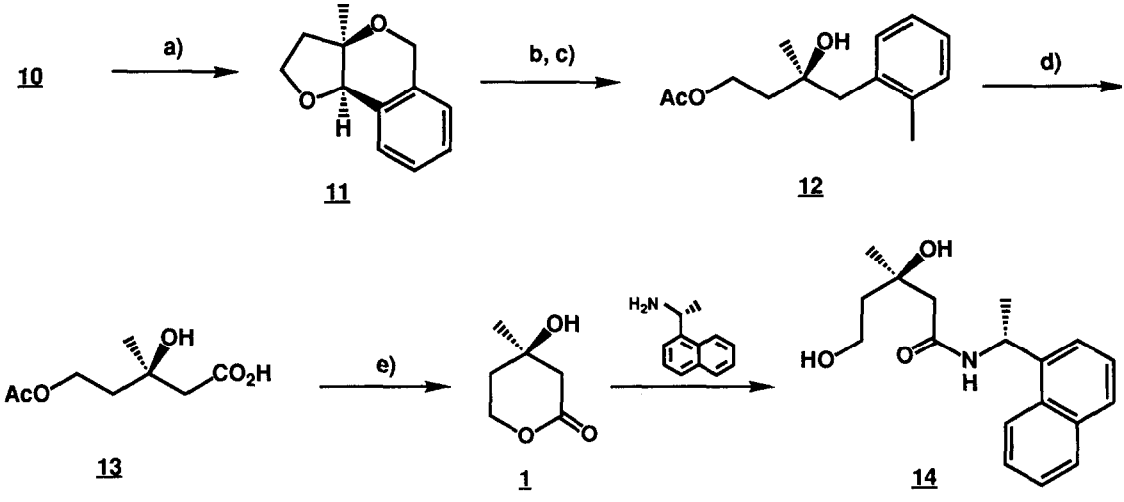


a) O_3/MeOH; $NaBH_4$; b) DIBAL

Scheme 3. Attempted chain-elongation

The final solution to this problem was obtained by an unexpected reaction shown below. When boron trifluoride etherate, a Lewis acid, was added for the activation of lactol to the mixture of **10** and the dithioacetal-stabilized phosphonate carbanion, a new spot appeared on the thin layer chromatogram of the reaction mixture. The NMR study including nuclear Overhauser experiment revealed the struc-

ture to be (4bR,7aR)-(+)-7a-methyl-4b,7,7,7a-tetrahydrofuro[3,2-c]1H-2-benzopyran (**11**, Fig. 1), which is composed of a single diastereomer judged from ^{13}C NMR spectrum. Moreover, this product was cleanly obtained from **8** as well as in the absence of nucleophile in 96.2% yield. This product is obviously derived via an intramolecular Friedel-Crafts type reaction, the related examples of which had appeared in the glycosidation of sugar derivatives.[16] This reaction provided us a clue to the completion of the planned synthesis. The product **11** was hydrogenated in the presence of palladium on carbon in acetic acid followed by acetylation to give acetate **12** in 94.4% yield (Scheme 4). In the present case, it is noteworthy that carbon chain elongation has been achieved by the aid of protecting group without adding any special carbon source.



a) $BF_3 \cdot OEt_2$; b) H_2, Pd-C/AcOH; c) Ac_2O/pyridine; d) O_3/acetone; H_2O_2; e) aq K_2CO_3; H^+

Scheme 4. Synthesis of (R)-Mevalonolactone

The next task to be done is the degradation of an aromatic ring into carboxylic acid. As the solvent for the ozonolysis of acetate **12**, acetone was utilized, considering the acid lability of **12**. Subsequent oxidative work-up using hydrogen peroxide gave a crude acid **13**,[4] which was hydrolyzed using aqueous potassium carbonate. After acidification and extraction, (R)-(-)-mevalonolactone (**1**) was obtained in 32.4% yield from **12**, $[\alpha]_D^{24}$ -18.4° (c=1.2, ethanol) [lit.[1] $[\alpha]_D^{20}$ -19.9° (ethanol)]. Inspection of the corresponding (R)-1-(1'-naphthyl)ethyl amide **14** by 400 MHz ^1H NMR showed that the e.e. of the present sample to be 94~95%. The

partial racemization might be ascribable to the final hydrolysis,[4i] although its extent was considerably suppressed in the present case.

In conclusion, (R)-(-)-mevalonolactone was synthesized from ester **5** in 7 steps with 21.5% overall yield, utilizing an intramolecular Friedel-Crafts reaction as the key-step. The utility of ester **5** as a chiral carbon source was further demonstrated by the present synthesis, as well as by the synthesis of (-)-frontalin.[12]

EXPERIMENTAL

All b.ps were uncorrected. IR spectra were measured as films for oils on a Jasco IRA-202 spectrometer. ^{1}H NMR spectra were recorded with TMS as an internal standard and $CDCl_3$ as a solvent at 90 MHz on a JPOL JNM FX-90 spectrometer or at 400 MHz on a JEOL JNM GX-400 spectrometer. ^{13}C NMR spectrum was recorded with TMS as an internal standard at 100 MHz on a JEOL JNM GX-400 spectrometer. Optical rotations were measured on a Jasco DIP 360 polarimeter and with $CHCl_3$ as solvent unless otherwise stated. Mass spectra were recorded on a Hitachi M-80 at 70 eV. TLC analyses were performed with Merck Kieselgel 60 F_{254} (Art 5715). Wako Gel B-5F and silica gel 60 K070-WH (70-230 mesh) of Katayama Chemical Co. were used for preparative TLC and column chromatography, respectively.

(R)-(-)-2-Benzyloxy-2-methyl-4-butanolide **9**. Ozone was bubbled into a stirred soln of **5** [$[\alpha]_D^{25}$ +3.8° (c=1.63), >99% e.e.,[12] 1.40 g, 5.98 mmol] in MeOH (42 ml) for 1.5 h at -78°C. Excess ozone was purged by bubbling Ar into the soln. $NaBH_4$ (1.47 g, 38.8 mmol) was added to the mixture at -78°C, and the stirring was continued overnight with gradually raising the temperature. Then the excess $NaBH_4$ was destroyed by the addition of AcOH (1.2 ml), and the mixture was concentrated in vacuo. After the addition of water, the residue was extracted with Et_2O. The extract was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane-EtOAc, 5:1) to give **9** (1.06 g, 86.2%), $[\alpha]_D^{22}$ -18.9° (c=1.83); νmax 1780, 1500, 1195, 1145, 1095, 1050, 1020, 920, 740, 700 cm^{-1}; δ 1.56 (3H, s), 2.11~2.52 (2H, m), 4.23~4.47 (2H, m), 4.59 (3H, s), 7.32 (5H, br.s); MS: m/z 100 (M^++1-BnO, 85%), 91 ($C_7H_7^+$, 100%).

(2RS,3R)-3-Benzyloxy-3-methyltetrahydrofuran-2-ol **10**. A soln of DIBAL (1.14 M in hexane, 8.9 ml, 10.1 mmol) was added dropwise to the stirred soln of **9** (1.50 g, 7.27 mmol) in dry THF (15 ml) at -78°C under Ar. After stirring for 1.5 h at -78°C, the mixture was quenched by sat NH_4Cl soln and extracted with Et_2O. The extract was washed with water, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane-EtOAc, 5:1~3:1) to give **10** (1.28 g, 84.8%), $[\alpha]_D^{22}$ -36.4° (c=1.01); νmax 3400, 1500, 1140, 1040, 995, 935, 700 cm^{-1}; δ 1.45 (1.0H, s), 1.47 (2.0H, s), 1.93-2.46 (2H, m), 3.82-4.15 (2H, m), 4.50 (1.3H, s), 4.55 (0.7H, s), 5.01 (0.3H, d, J=7.9 Hz), 5.24 (0.7H, d, J=3.1 Hz), 7.31~7.33 (5H, m). This was employed in the next step without further purification.

(4bR,7aR)-(+)-7a-methyl-4b,7,7,7a-tetrahydrofuro[3,2-c]1H-2-benzopyran **11**. $BF_3{\cdot}OEt_2$ (0.87 ml, 8.9 mmol) was added dropwise to a stirred soln of **10** (1.23 g, 5.90 mmol) in dry CH_2Cl_2 (15 ml) at 0°C under Ar. After stirring for 1.5 h at room temp, the mixture was quenched by water, and extracted with Et_2O. The extract was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane-EtOAc, 3:1) followed by distillation to give **11** (1.08 g, 96.2%), b.p. 160~170°C/1.7 Torr (bulb-to-bulb); $[\alpha]_D^{22}$ +67.7° (c=1.01); νmax 2980, 2850, 1500, 1440, 1375, 1215, 1130, 1110, 1080, 1040, 1000, 780, 745 cm^{-1}; δ (400 MHz) 1.40 (3H, s, Hh), 2.15 (1H, ddd, J=4.4, 7.8, 14.3 Hz, Hg), 2.28 (1H, ddd, J=4.4, 7.8, 14.3 Hz, Hf), 3.93 (1H, ddd, J=4.4, 7.8, 7.8 Hz, Hd), 4.12 (1H, ddd, J=4.8, 7.8, 7.8 Hz, He), 4.32 (1H, s, Hc), 4.76 and 4.81 (each 1H, d, J=15.7 Hz, Hab), 7.07~7.09 (1H, m), 7.26~7.30 (2H, m), 7.40~7.42 (1H, m); NOE (400 MHz, $CDCl_3$) Hh irradiation: Hc 11.7%, Hg 8.9%; Hc irradiation: Hh 3.7%, Hg 0.9%; Hd 1.6% gain; δ (^{13}C, $CDCl_3$) 19.03, 41.03, 62.49, 66.55, 78.90, 79.55, 124.04, 127.10, 128.19, 130.71, 130.88, 134.28; MS: m/z 190.0989 (M^+). Calc for $C_{12}H_{14}O_2$: 190.0992.

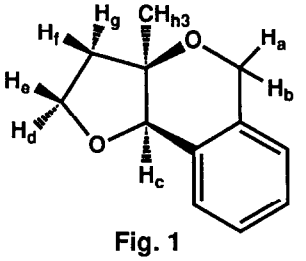


Fig. 1

(S)-(-)-3-Hydroxy-3-methyl-4-(2'-methylphenyl)butyl acetate **12**. A mixture of **11** (1.00 g, 5.26 mmol) and Pd-C (10%, 340 mg) in AcOH (90 ml) was vigorously stirred under H_2 for 64 h at room temp. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in dry C_5H_5N (10 ml) and to this mixture was added Ac_2O (1.07 g, 10.5 mmol) at 0°C. After stirring for 4 h at room temp, the mixture was diluted with Et_2O, poured into ice-water and stirred for 30 min at room temp. The Et_2O layer was separated and washed with sat $CuSO_4$ soln, brine and sat Na_2SO_4 soln, dried ($NaSO_4$), and concentrated in vacuo. The residue was purified by

silica gel column chromatography (hexane-EtOAc, 4:1) to give **12** (1.12 g, 94.4% from **11**), $[\alpha]_D^{22}$ -15.9° (c=1.18); νmax 3480, 1735, 1490, 1240, 1130, 1030, 940, 740 cm^{-1}; δ 1.21 (3H, s), 1.58 (1H, br.s), 1.91 (2H, dd, J=7.1, 7.1 Hz), 2.06 (3H, s), 2.36 (3H, s), 2.80 (1H, d, J=13.7 Hz), 2.88 (1H, d, J=13.7 Hz), 4.27 (1H, dt, J=7.1, 14.2 Hz), 2.43 (1H, dt, J=7.1, 14.2 Hz), 7.14~7.20 (4H, m); MS: m/z 106.0760 (fragment). Calc for C_8H_8 (CH_3-C_6H_4-CH_3) 106.0781.

(R)-(-)-Mevalonolactone **1**. Ozone was bubbled into a stirred soln of **12** (400 mg, 1.69 mmol) in acetone (25 ml) for 9 h at room temp. Then the excess ozone was purged by bubbling Ar into the soln. H_2O_2 (35%, 2 ml) was added dropwise to the stirred soln at 0°C. After stirring overnight at room temp, the excess H_2O_2 was destroyed by the addition of a catalytic amount of Pt black and the stirring was further continued for additional 5 h. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was mixed with water (5 ml) and K_2CO_3 (0.5 g) at 0°C and the mixture was stirred overnight at room temp. It was then cooled to 0~5°C and acidified to pH 3 by the addition of 6N HCl, and stirred for 1 h at room temp. The mixture was extracted with $CHCl_3$ (20 mlx15) after saturation with NaCl. The extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (hexane-EtOAc, 1:4) followed by distillation to give **1** (71.3 mg, 32.4% from **12**), b.p. 170~180°C/2.0 Torr (bulb-to-bulb); $[\alpha]_D^{24}$ -18.4° (c=1.20, EtOH); νmax 3450, 2980, 2950, 1720, 1480, 1400, 1305, 1265, 1240, 1160, 1135, 1070, 1015, 990, 940, 880, 805 cm^{-1}; δ (400 MHz), 1.41 (3H, s), 1.75 (1H, br.s), 1.87~1.94 (2H, m), 2.54 (1H, d, J=17.6 Hz), 2.76 (1H, dd, J=1.7, 17.6 Hz), 4.36 (1H, ddd, J=3.9, 4.9, 11.4 Hz), 4.61 (1H, ddd, J=4.9, 9.8, 11.4 Hz); MS: m/z 131 (M^++1, 22%), 115 (M^++1-CH); MS: m/z 115.0397 (fragment). Calc for $C_5H_7O_3$ (M^++1-CH_3): 115.0394. Its IR and 400 MHz NMR spectra were identical with those of an authentic racemic sample.

Determination of the enantiomeric excess of **1**. According to the reported procedure,[17] (±)-**1** (purchased from Tokyo Kasei Co., Japan) was converted to the corresponding (R)-1-(1'-naphthyl)ethyl amide **14**; δ (400 MHz) 1.279 and 1.295 (each s, total 3H). The amide from (R)-(-)-**1**, the signals at δ 1.279 and 1.295 was in a ratio of 1.0:34.5. Therefore, the enantiomeric excess of (R)-(-)-**1** was determined to be 94~95%.

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