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CONCISE FORMAL SYNTHESIS OF (*S*)-GREGATIN B

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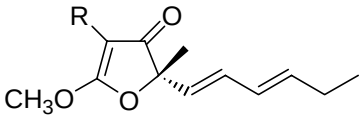
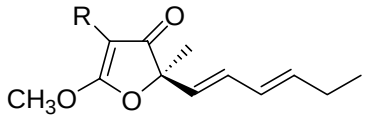
Abstract-(*S*)-3-Acetyl-5-[(1*E*,3*E*)-1,3-hexadienyl]-4-hydroxy-5-methyl-2(5*H*)-furanone, known precursor for the synthesis of (*S*)-gregatin B, was synthesized in a fewer steps and higher overall yield starting from (*R*)-lactic acid.

(*S*)-Gregatins A, B[1] and (*R*)-aspertetronins A, B[2] were isolated from *Cephalosporium gregatum* and *Aspergillus panamensis*, respectively, as antimicrobial metabolites and phytotoxic substances.[3] They are regarded as the derivatives of 3-acyltetronic acid which possesses the same side chain at C5, although the chirality is different (Figure 1). On the synthetic research of these compounds, only one report for the synthesis of (*S*)-gregatin B appeared in 1984,[4] but the multi-steps were required and the total yield was relatively low.



R=COCH=CHCH$_3$ [(*S*)-Gregatin A]

R=COCH$_3$ [(*S*)-Gregatin B]

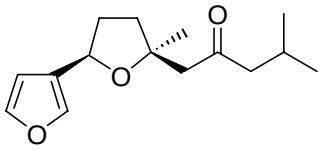


R=COCH=CHCH$_3$ [(*R*)-Aspertetronin A]

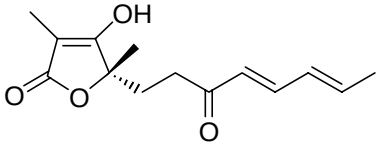
R=COCH$_2$CH(OH)CH$_3$ [(*R*)-Aspertetronin B]

Figure 1

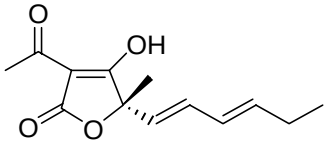
In the course of our synthetic studies on biologically active natural products, which possess chiral quaternary center accompanying with one oxygen function, we have synthesized (+)-ipomeamarone[5] and (-)-vertinolide[6] by adapting the chiral self-reproduction method developed by Seebach *et al*.[7]



(+)-Ipomeamarone



(-)-Vertinolide

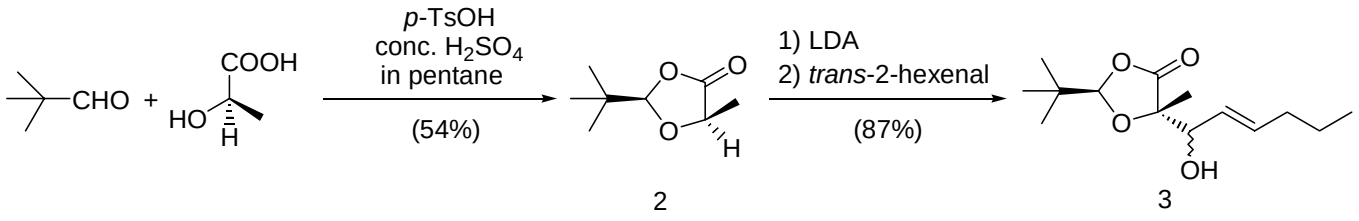


1

Figure 2

In continuation of that line, we planned to synthesize (*S*)-3-acetyl-5-[(1*E*,3*E*)-1,3-hexadienyl]-4-hydroxy-5-methyl- 2(5*H*)-furanone (**1**),[4, 8] known precursor for the synthesis of (*S*)-gregatin B, in a fewer steps and higher yield. Conversion of **1** to (*S*)-gregatin B using diazomethane in the presence of BF_3-etherate was reported by Takaiwa and Yamashita.[4]

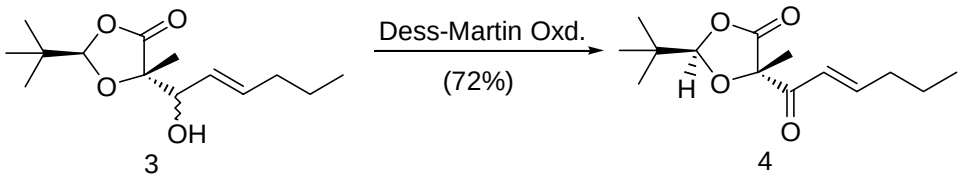
For the synthesis of **1**, (2*R*,5*R*)-2-(1,1-dimethylethyl)-5-methyl-1,3-dioxolan-4-one (**2**)[6, 7] was selected as the starting material, which was readily derived from (*R*)-lactic acid[9] and 2,2-dimethylpropanal. The addition of the enolate derived from **2** to *trans*-2-hexenal occurred stereoselectively from α-side to give the alcohol (**3**) as a 1:1 mixture of diastereomers concerning with the orientation of the hydroxyl group (Scheme 1).



2 3

Scheme 1

In order to confirm the stereochemistry of the newly formed chiral center at C5 of **3**, it was converted to the enone (**4**) by oxidation with Dess-Martin periodinane.[10] In the ^{1}H-NMR spectrum of **4**, no NOE was observed between C2 methine proton and C5 methyl group (Scheme 2). This result indicates that the stereochemistry at C5 is *S*.

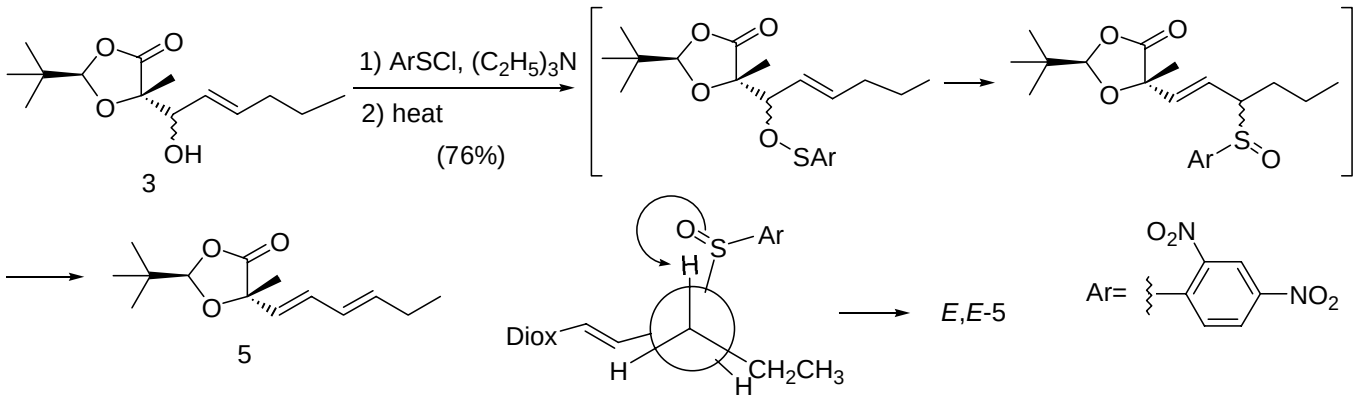


3 4

Scheme 2

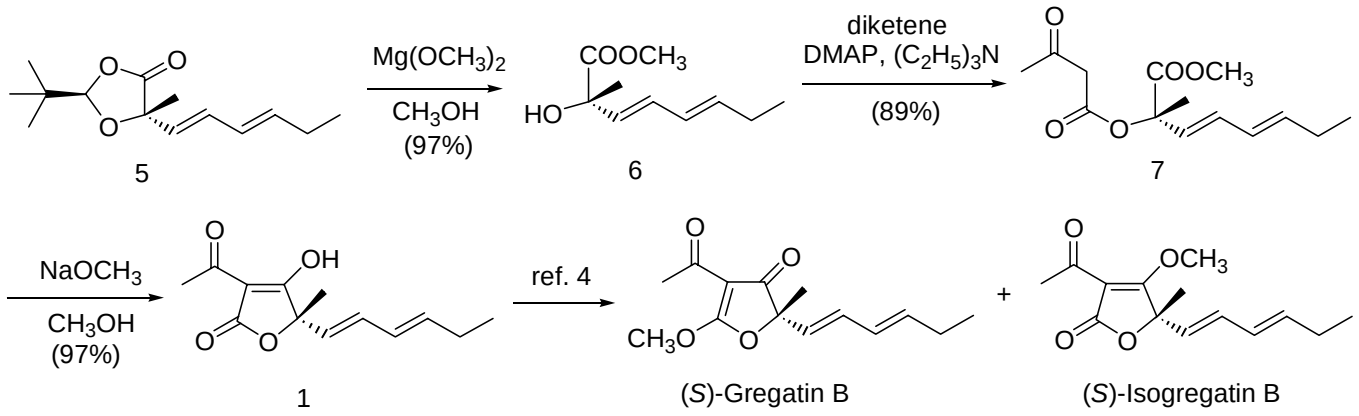
Transformation of the allyl alcohol (**3**) to *E*,*E*-1,3-diene (**5**) was examined. After several fruitless trials including, for example, mesylation of **3** and elimination with base or base treatment of the tosylhydrazone of **4** (Bamford-Stevens reaction or Shapiro reaction), [2,3] sigmatropic rearrangement of the sulfenate of **3** to the sulfoxide and its thermal syn elimination[11] were performed. Thus, the treatment of **3** with 2,4-dinitrophenylsulfenyl chloride in the presence of triethylamine gave the sulfenate, which rearranged to form the sulfoxide, and the successive thermal syn elimination of the sulfoxide occurred to afford exclusively *E*,*E*-**5** in 76% yield. The required conformation for the syn elimination of the sulfoxide is favorable to give the *E*,*E*-diene as shown below (Scheme 3).

For the construction of 3-acetyltetronic acid skeleton, the dioxolanone (**5**) was first treated with magnesium methoxide to form the hydroxy ester (**6**) in 97% yield, which was successively acylated with diketene in the presence of 4-dimethylaminopyridine (DMAP) and triethylamine to provide the keto diester (**7**) in 89% yield. The final condensation reaction of **7** was examined by the three different



Scheme 3

methods, 1) triethylamine in acetone,[4] 2) tetrabutylammonium fluoride in THF,[12] and 3) sodium methoxide in methanol.[13] Among them, the method 1 took long reaction time and resulted in lower yield. On the other hand, the methods 2 and 3 worked well, in the shorter reaction time and higher yields, but in the case of method 2, difficulties were observed in purification step using silica gel flash column chromatography. The method 3 was the best, and the reaction completed within 30 min and the yield of the desired compound (**1**) was 97% (Scheme 4). IR, ^{1}H-NMR and MS spectral data were identical with those of the reported racemic **1**.[8] Takaiwa and Yamashita have reported the transformation of **1** to (*S*)-gregatin B and (*S*)-isogregatin B using diazomethane in the presence of BF_3-etherate.[4] Therefore, we have completed the concise formal synthesis of (*S*)-gregatin B.



Scheme 4

In conclusion, we synthesized (*S*)-3-acetyl-5-[(1*E*,3*E*)-1,3-hexadienyl]-4-hydroxy-5-methyl-2(5*H*)-furanone (**1**), known precursor for the synthesis of (*S*)-gregatin B, in 6 steps and 30% overall yield starting from (*R*)-lactic acid (the reported method[4]: 12 steps and 0.83% overall yield starting from (*S*)-tetrahydro-2-methyl-5-oxo-2-furancarboxylic acid[14]).

EXPERIMENTAL

IR spectra were measured with a Hitachi 260-30 or JASCO FT/IR-460 plus infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-GSX270 (270 MHz) or JEOL JNM-ECA500 (500 MHz) spectrometer using tetramethylsilane as the internal standard. MS and high-resolution MS spectra (HRMS) were measured with a JEOL JMS-700TKM instrument at 70 eV. Optical rotation was measured with JASCO DIP-370 polarimeter.

(2*R*,5*S*)-2-*tert*-Butyl-5-(1-hydroxy-2-hexenyl)-5-methyl-1,3-dioxolan-4-one (3)

A solution of **2** (4.13 g, 15.3 mmol) in THF (20 mL) was added dropwise under stirring to a THF solution of LDA [prepared from diisopropylamine (4.43 mL, 31.6 mmol), *n*-C_4H_9Li (19.4 mL, 30.9 mmol, 1.59 M hexane solution, and THF (160 mL)] at -78 ℃, and the mixture was stirred for 45 min. To the obtained solution was added dropwise under stirring a solution of *trans*-2-hexenal (4.40 g, 37.7 mmol) in THF (16 mL) at that temperature, and the mixture was stirred for 55 min at -78 ℃. After the mixture was warmed up to rt, half saturated NH_4Cl solution was added and the mixture was extracted with ether. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an oil which was purified by SiO_2 flash column chromatography (hexane:ether=4:1) to give **3** (5.64 g, 87%) as a pale yellow oil. IR (neat): 3480, 1793, 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, m, CH_3), 0.95 (9H, s, $C(CH_3)_3$), 1.37 (3H, s, $CH_2C\underline{H}_3$), 1.40-1.45 (2H, m, $C\underline{H}_2CH_3$), 1.92 (1H, br s, OH), 2.01-2.11 (2H, m, $=CHC\underline{H}_2$), 4.20-4.25 (1H, m, C<u>H</u>OH), 5.41 (1H, s, OCHO), 5.56-5.84 (2H, m, CH=CH). MS (*m/z*): 158, 125, 87, 70, 57, 43.

(2*R*,5*S*)-2-*tert*-Butyl-5-(2-hexenoyl)-5-methyl-1,3-dioxolan-4-one (4)

A solution of **3** (4.70 g, 18.5 mmol) in CH_2Cl_2 (18.2 mL) was added dropwise under stirring to the solution of Dess- Martin periodinane (15 wt % in CH_2Cl_2, 55.8 mL, 26.8 mmol) and the solution was heated under reflux for 1.5 h. After cooling down, the mixture was diluted with ether (107 mL) and saturated $NaHCO_3$ (107 mL) solution containing Na_2SO_3 (26.75 g), and stirred for 5 min. After separation of the layers, the water layer was extracted with ether. The combined organic layer was washed with saturated $NaHCO_3$ solution, water, and brine, successively, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an oil which was purified by SiO_2 flash column chromatography (hexane:ether=2:1) to afford **4** (3.35 g, 72%) as a pale yellow oil. IR (neat): 1797, 1704, 1626 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, *J*=7.0 Hz, $CH_2C\underline{H}_3$), 1.00 (9H, s, $C(CH_3)_3$), 1.52 (2H, sextet, *J*=7.0 Hz, $C\underline{H}_2CH_3$), 1.66 (3H, s, CH_3), 2.21-2.29 (2H, m, $C\underline{H}_2CH_2CH_3$), 5.21 (1H, s, OCHO), 6.55 (1H, dt, *J*=15.3, 1.65 Hz, C<u>H</u>=$CHCH_2$), 7.16 (1H, dt, *J*=15.3, 7.0 Hz, CH=C<u>H</u>CH_2). HRMS (*m/z*) Calcd for $C_{14}H_{22}O_4$: 254.1518. Found: 254.1526.

(2*R*,5*S*)-2-*tert*-Butyl-5-[(1*E*,3*E*)-1,3-hexadienyl]-5-methyl-1,3-dioxolan-4-one (5)

To a solution **3** (5.00 g, 19.5 mmol) in CH_2Cl_2 (176 mL) were added under stirring $(C_2H_5)_3N$ (7.1 mL, 50.7 mmol) and 2,4-dinitrobenzenesulfenyl chloride (10.98 g, 46.8 mmol) and the mixture was heated under reflux for 3 h. After cooling down to rt, pentane was added to form precipitates, which were removed by filtration. The filtrate was concentrated under reduced pressure to give an oil which was purified by SiO_2 flash column chromatography (hexane:ether=79:1) to afford **5** (3.53 g, 76%) as a pale

yellow oil. IR (neat): 1793, 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (9H, s, $C(CH_3)_3$), 1.05 (3H, t, *J*=7.0 Hz, $CH_2C\underline{H}_3$), 1.52 (3H, s, CH_3), 2.06-2.17 (2H, m, $=CHC\underline{H}_2$), 5.14 (1H, s, OCHO), 5.52 (1H, d, *J*=15.5 Hz, $C\underline{H}$=CH-CH=CH_2), 5.84 (1H, dt, *J*=15.5, 6.5 Hz, CH=$C\underline{H}CH_2$), 6.03 (1H, tdd, *J*=15.5, 10.5, 2.0 Hz, =CH-$C\underline{H}$=$CHCH_2$), 6.30 (1H, dd, *J*=15.5, 10.5 Hz, CH=$C\underline{H}$-CH=$CHCH_2$). $[\alpha]_D^{26}$: -77.85° (*c*=0.009, CH_3OH). HRMS (*m/z*) Calcd for $C_{14}H_{22}O_3$: 238.1569. Found: 238.1577. *Anal*. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.31. Found: C, 70.69; H, 9.25.

(*S*)-(3*E*,5*E*)-Methyl 2-hydroxy-2-methyl-3,5-octadienoate (6)

To a solution of $Mg(OCH_3)_2$ in CH_3OH [prepared from Mg (460 mg, 18.9 mg atom), CH_3OH (10 mL), and small amount of CCl_4] was added dropwise under stirring a solution of **5** (1.50 g, 6.3 mmol) in THF at 0 ℃. The reaction mixture was stirred and warmed gradually up to rt over a period of 25 min and then the stirring was continued for 1.5 h at 30 ℃. After addition of saturated NH_4Cl solution, the mixture was extracted with $AcOC_2H_5$. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave **6** (1.12 g, 97%) as a colorless oil. IR (neat): 3510, 1738, 1657 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, *J*=7.4 Hz, $CH_2C\underline{H}_3$), 1.50 (3H, s, CH_3), 2.11 (2H, m, $=CHC\underline{H}_2$), 3.78 (3H, s, $COOCH_3$), 5.69 (1H, d, *J*=15.3 Hz, $C\underline{H}$=CH-CH=), 5.79 (1H, dt, *J*=15.3, 6.5 Hz, CH=$C\underline{H}CH_2$), 6.03 (1H, tdd, *J*=15.3, 10.3, 2.0 Hz, CH=CHC$\underline{H}$=CH), 6.38 (1H, dd, *J*=15.3, 10.5 Hz, CH=$C\underline{H}$CH=). $[\alpha]_D^{26}$: -11.53° (*c*=0.011, CH_3OH). HRMS (*m/z*) Calcd for $C_{10}H_{16}O_3$: 184.1099. Found: 184.1100.

(*S*)-Methyl 2-(3-oxobutanoyloxy)-2-methyl-(3*E*,5*E*)-3,5-octadienoate (7)

To a solution of **6** (787 mg, 4.3 mmol) and DMAP (47 mg 0.34 mmol) in ether (17.5 mL) was added dropwise diketene (0.43 mL, 5.7 mmol) at rt under stirring and then the mixture was stirred for 50 min at rt. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by SiO_2 flash column chromatography (hexane:ether=4:1) to afford **7** (1.02 g, 89%) as a colorless oil. IR (neat): 1747, 1722, 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, *J*=7.5 Hz, $CH_2C\underline{H}_3$), 1.71 (3H, s, CH_3), 2.01-2.14 (2H, m, $=CHC\underline{H}_2$), 2.29 (3H, s, CH_3), 3.47 (2H, s, $COCH_2CO$), 3.74 (3H, s, $COOCH_3$), 5.82 (1H, d, *J*=15.5 Hz, $C\underline{H}$=CHCH=), 5.84 (1H, dt, *J*=15.5, 6.5 Hz, CH=$C\underline{H}CH_2$), 6.03 (1H, tdd, *J*=15.5, 10.3, 2.0 Hz, CH=CHC$\underline{H}$=), 6.31 (1H, dd, *J*=15.5, 10.3 Hz, CH=$C\underline{H}$CH=). $[\alpha]_D^{26}$: -30.55° (*c*=0.013, CH_3OH). HRMS (*m/z*) Calcd for $C_{14}H_{20}O_5$: 268.1311. Found: 268.1325.

(*S*)-3-Acetyl-5-[(1*E*,3*E*)-1,3-hexadienyl]-4-hydroxy-5-methyl-2(5*H*)-furanone (1)

To a solution of $NaOCH_3$ [prepared from Na (14 mg, 0.61 mg atom) and CH_3OH (1 mL)] was added under stirring a solution of **7** (109.6 mg, 0.41 mmol) in CH_3OH (3 mL) over a period of 10 min and then the reaction mixture was heated under reflux for 30 min. After concentration of the mixture under reduced pressure, to the residue was added 2N HCl (1.5 mL). The mixture was salted out and extracted with $CHCl_3$. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave **1** (93.4 mg, 97%) as a pale yellow oil. IR (neat): 1768, 1696, 1662, 1614 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, *J*=7.4 Hz, $CH_2C\underline{H}_3$), 1.58 (3H, s, CH_3), 2.06-2.16 (2H, m, $=CHC\underline{H}_2$), 2.54 (3H, s, $COCH_3$), 5.60 (1H, d, *J*=15.3 Hz, $C\underline{H}$=CHCH=), 5.84 (1H, dt, *J*=15.3, 6.5 Hz,

CH=C<u>H</u>CH$_2$), 5.96-6.05 (1H, m, CH=CHC<u>H</u>=), 6.37 (1H, dd, *J*=15.3, 10.1 Hz, CH=C<u>H</u>CH=), 11.16 (1H, br s, OH). $[\alpha]_D^{24}$: -128.46^o (*c*=0.011, $CHCl_3$). HRMS (*m/z*) Calcd for $C_{13}H_{16}O_4$: 236.1049. Found: 236.1045.

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