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Formal synthesis of (−)-anisomycin based on stereoselective nucleophilic substitution along with 1,2-aryl migration☆

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Abstract—The stereoselective conversion of (4*R*)-5-hydroxy-4-(4′-methoxyphenyl)-2(*E*)-pentenoate **4** into the (4*S*)-4-hydroxy-5-(4′-methoxyphenyl)-2(*E*)-pentenoate **5** using the $AgNO_3$/MS 4 Å/$MeNO_2$ system was accomplished along with complete inversion at the C_4-position, and the synthesis of the intermediate (4*S*)-**7** for the chiral synthesis of (−)-anisomycin **6** from (4*S*)-**7** based on osmium tetroxide-catalyzed stereoselective hydroxylation was achieved.

1. Introduction

We previously reported that silica gel promotes the γ-lactonization and the concomitant 1,2-aryl migration of 4-aryl-5-tosyloxy pentanoate **1** to give γ-lactone **2** along with complete inversion in high yield.[2] In the case of this reaction, an intramolecular attack of the ester carbonyl group to the σ-bridged phenonium ion **A** proceeded selectively at the C_4-position to provide the γ-lactone. If the 4-aryl-5-tosyloxy-2(*E*)-pentenoate **3** is subjected to solvolysis in the presence of a nucleophile, 1,2-aryl migration followed by intermolecular nucleophilic substitution along with inversion at the C_4-position should occur to afford the 5-aryl-4-substituted-2(*E*)-pentenoate derivatives **B**. However, this type of reaction has not been reported so far. In this paper, we wish to report both the possibility of the above-mentioned reaction and its stereochemical course. After the reaction was established, we describe the stereoselective conversion of (4*R*)-5-hydroxy-4-(4′-methoxyphenyl)-2(*E*)-pentenoate **4** into the (4*S*)-4-hydroxy-5-(4′-methoxyphenyl)-2(*E*)-pentenoate **5** and its application to the formal total synthesis of (−)-anisomycin **6** via synthetic intermediate (4*S*)-**7**.

The antibiotic (−)-anisomycin **6**, isolated from the fermentation broth of *Streptomyces* sp., was reported to possess the 2*R*,3*S*,4*S* absolute configuration.[3] (−)-Anisomycin **6** exhibits strong and selective activity against pathogenic protozoa and fungi and has clinically been used with success in the treatment of vaginitis due to trichomonas vaginilis and of amoebic dysentery[3] (Scheme 1).

2. 1,2-Aryl migration under solvolysis condition

At first, 1,2-aryl migration along with the intermolecular nucleophilic substitution at the C_4-position using (±)-**4** and (±)-**8** was examined. The reported substrate (±)-**4**[4] was treated with Ts_2O to give the corresponding tosylate (±)-**9** (96% yield) which was subjected to solvolysis in water-saturated $MeNO_2$ to provide an inseparable mixture of (±)-**5** and (±)-**9**. This mixture was subjected to enzymatic hydrolysis using lipase OF-360 from *Candida rugosa* to afford the desired (±)-**5** (51% yield) together with the starting (±)-**9** (34% recovery). The structure of (±)-**5** was determined by NMR analysis and finally confirmed by conversion of (4*R*)-**4** into the synthetic intermediate (4*S*)-**7** for (−)-anisomycin **6** as described later in the text. The second substrate (±)-**8**[4] was also converted to the tosylate (±)-**10** (80% yield) which was subjected to solvolysis under the same conditions as for (±)-**9** to afford the 1,2-migration product (±)-**12** (53% yield). The structure of (±)-**12** was confirmed by NMR analysis and the similar spectrum of (±)-**12** to that of (±)-**5**. In the case of these reactions, the reaction rate was found to be sluggish at 90 °C for 2–4 d. It was apparent that there was no difference in reactivity between the substrates (±)-**9** and (±)-**10** (Scheme 2).

Then, the leaving group in the substrate (±)-**4** was exchanged to a bromo group. Bromination of (±)-**4** gave

☆ See Ref. 1.

Keywords: (−)-Anisomycin; 1,2-Aryl migration; Phenonium ion.
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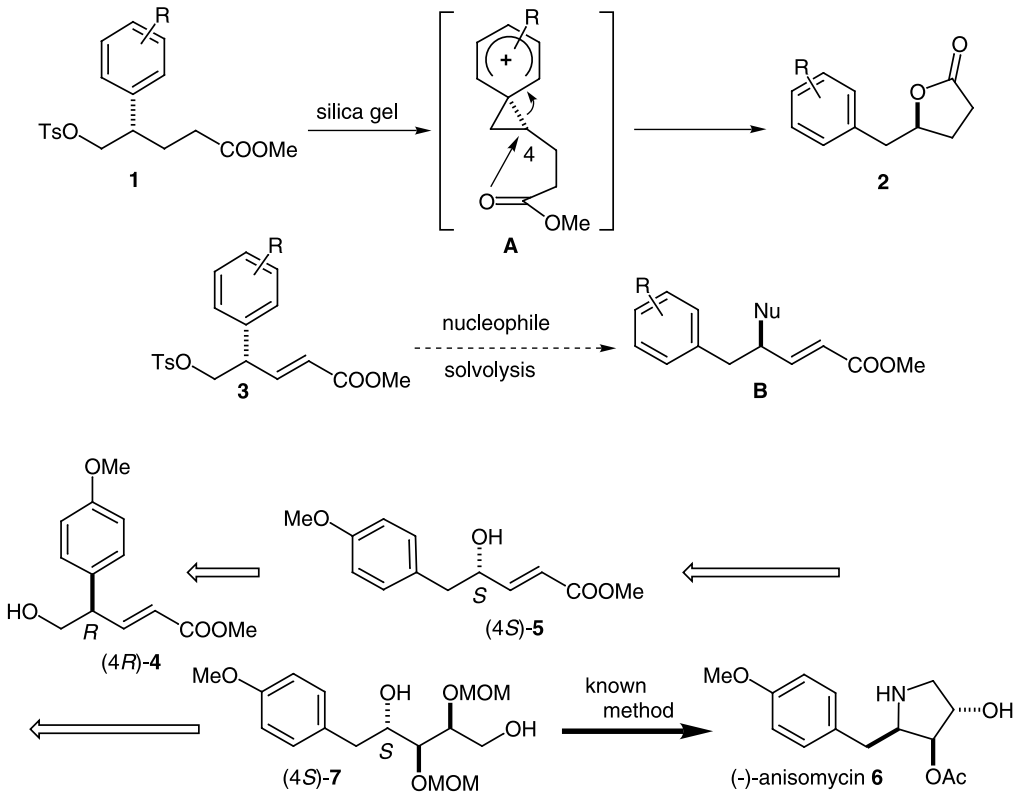
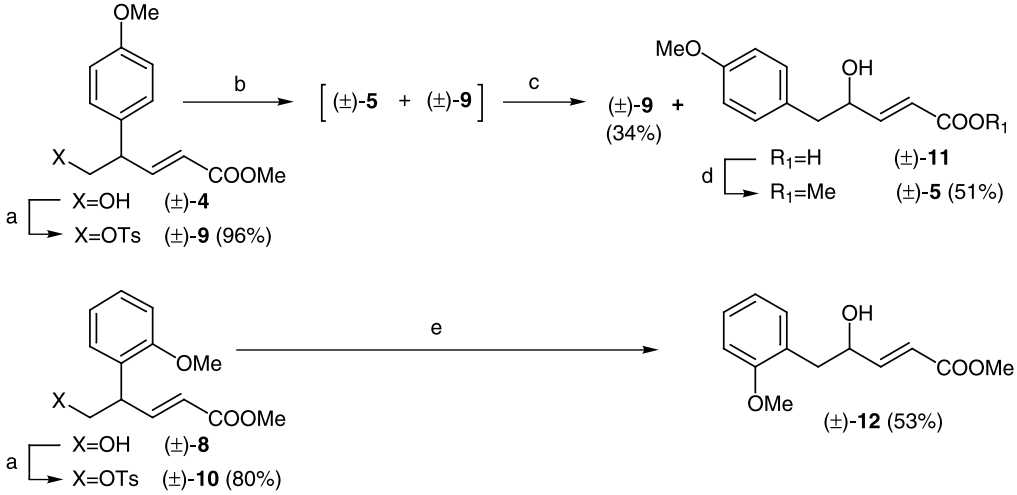


Scheme 1.

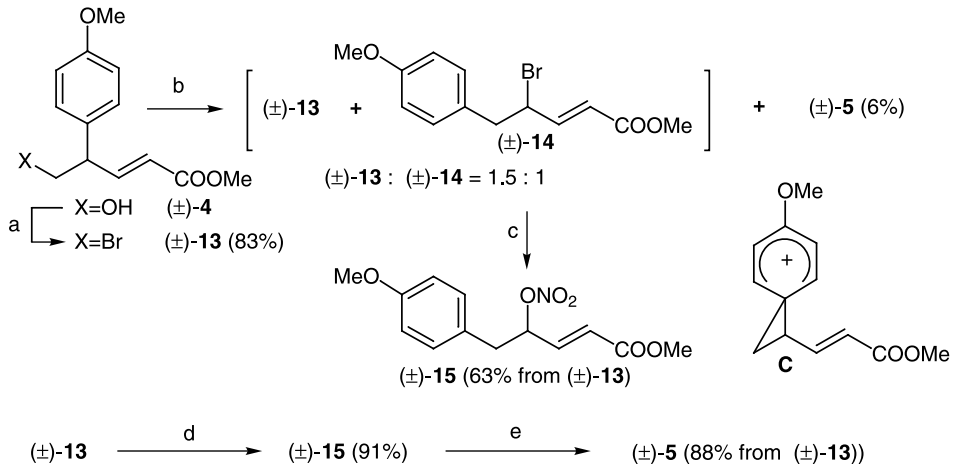
the corresponding bromide (±)-**13**[5] (83% yield) which was subjected to solvolysis in the same manner as in the case of (±)-**9** to afford (±)-**5** (6% yield) and an inseparable mixture (±)-**13**:(±)-**14**=1.5:1) of the starting (±)-**13** and an aryl migration product (±)-**14** (Scheme 3).

The structure of (±)-**14** could be determined by NMR analysis and the formation of (±)-**14** could be presumed to be attributed to the fact that the liberated bromo ion attacked again at the C(4)-position of the σ-bridged phenonium ion C to provide (±)-**14**. In order to confirm this presumption, conversion of the bromo group in (±)-**14** to an oxygen functional group was carried out. The above-mentioned mixture was treated with $AgNO_3$ in the presence of molecular sieves (MS 4 Å) at room temperature for 12 h to furnish the nitrate (±)-**15** in 63% overall yield from (±)-**13**. In order to check an effect on the silver salt, six kinds of silver salts were examined in H_2O–saturated $MeNO_2$ and the results are shown in Table 1.

In the cases of entries 1, 2, 3, 5 and 6, the desired (±)-**5** was obtained in moderate yield. In the case of using silver trifluoroacetate (entry 4) and silver nitrate (entry 7), trifluoroacetate (±)-**16** and nitrate (±)-**15** were obtained in addition to (±)-**5**, respectively. In terms of the reaction conditions and reagent usefulness, $AgNO_3$ was found to be a suitable reagent to trap the generated bromo ion. This result focuses on the direct formation of (±)-**15** from (±)-**13**.



Scheme 2. (a) Ts_2O/pyridine; (b) $H_2O/MeNO_2$, 90 °C, 2 d; (c) lipase OF-360; (d) CH_2N_2; (e) (1) $H_2O/MeNO_2$, 90 °C, 4 d; (2) CH_2N_2.



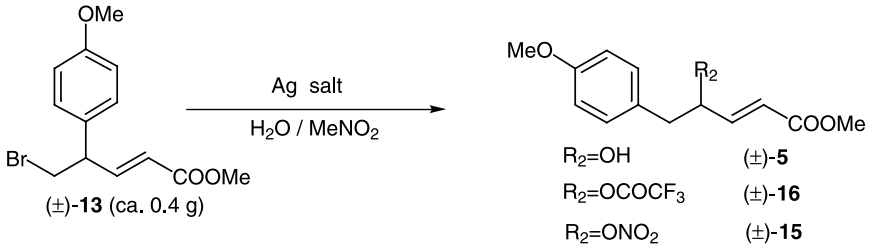
Scheme 3. (a) $CBr_4/Ph_3P/CH_3CN$; (b) $H_2O/MeNO_2$, 80 °C, 1 d; (c) $AgNO_3/MeNO_2$, MS 4 Å, rt, 12 h; (d) $AgNO_3/MeNO_2$, MS 4 Å, rt, 4 h; (e) $Zn/NH_4OAc/MeOH$, 0 °C, 1 h.

(Scheme 3) The reaction of (±)-**13** and $AgNO_3$, MS 4 Å in $MeNO_2$ at room temperature for 4 h yielded (±)-**15** (91% yield) which was treated with Zn and NH_4OAc in MeOH to give the desired (±)-**5** in 88% yield from (±)-**13**. This reaction was explained as follows. When substrates possessing a methoxyl group at least at the *ortho* and/or *para* positions of the phenyl group are applied, this type reaction should occur because electrophilicity of the presumed phenonium ion is adequately high. This presumption should be supported by the fact that tosylate **1** possessing a methoxyl group at least at the 2′, 4′ and 6′ positions of the phenyl ring afforded γ-lactone **2** in good yield.[2] From the above-mentioned experiment of this type reaction, $MeNO_2$ was regarded as the best reaction solvent and the presence of Ag^+ was essential. Oxygen nucleophiles such as the hydroxyl, trifluoroacetoxyl and nitrate groups were considered to be active, while nitrogen nucleophiles such as the azide ion, primary or secondary amines and phthalimide, and AgCN were inactive, to afford the starting (±)-**13**.

3. Confirmation of the stereochemical course and formal synthesis of (−)-anisomycin 6

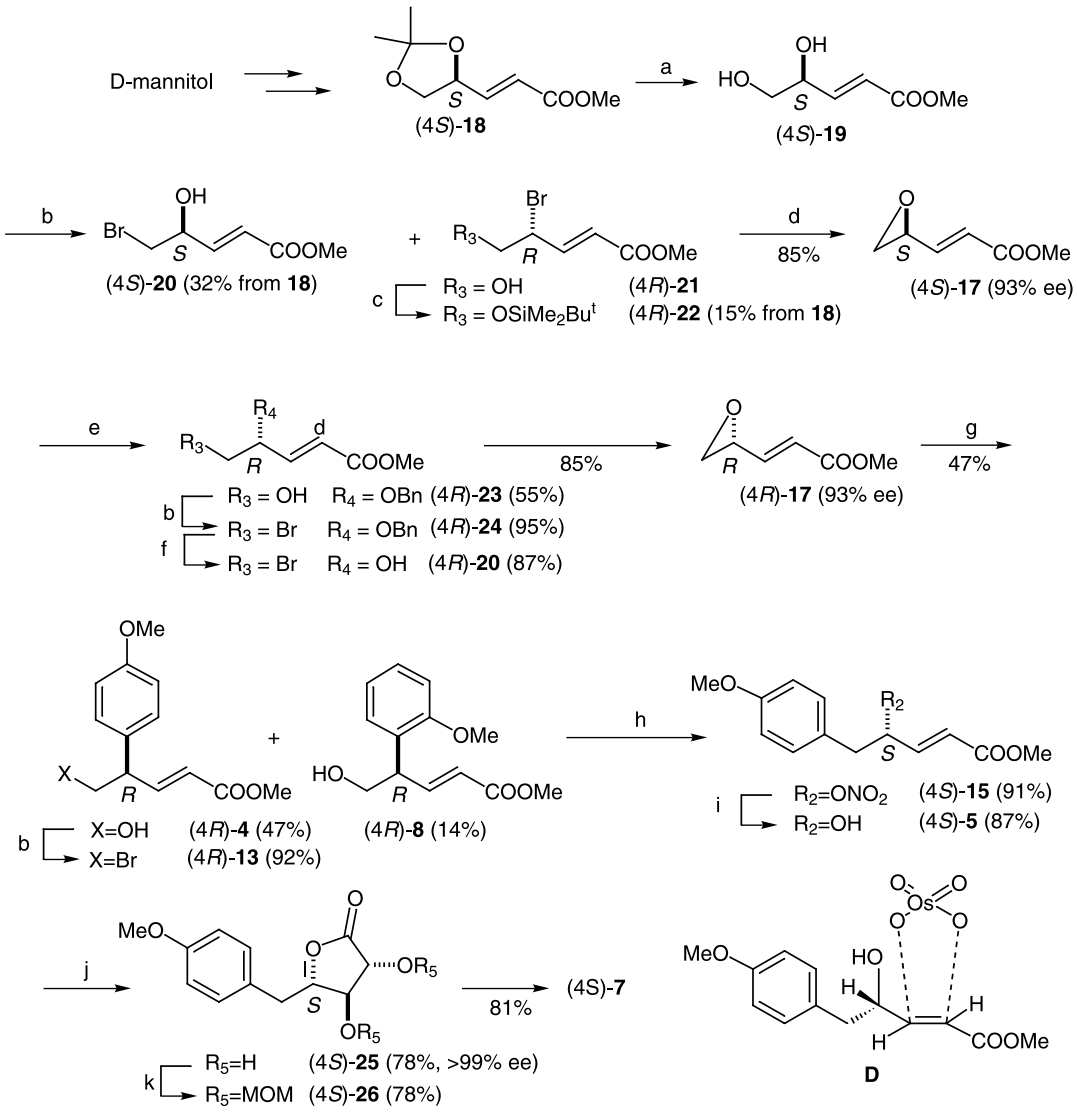
In order to clarify the stereochemical course of the above-mentioned reaction, the synthesis of (4*R*)-**4** from (4*R*)-4,5-epoxy-2(*E*)-pentenoate **17** is required because the reaction of (±)-**17** and anisole in the presence of $BF_3 \cdot Et_2O$ was reported to afford (±)-**4** as a main product.[4] (Scheme 4) The synthesis of (4*R*)-**17** was carried out by way of the following process from the commercially available (*E*)-unsaturated ester (4*S*)-**18**. By applying the reported procedure,[6] subsequent treatment of (4*S*)-**18** with 80% aqueous AcOH at 80 °C afforded the diol (4*S*)-**19** in quantitative yield. Bromination of (4*S*)-**19** with CBr_4 and triphenylphosphine in CH_2Cl_2 at reflux provided a mixture of bromohydrins (4*S*)-**20** and (4*R*)-**21**. This mixture was subjected to silylation followed by chromatographic separation to give the desired (4*S*)-**20** (32% overall yield from (4*S*)-**18**) and (4*R*)-**22** (15% overall yield from (4*S*)-**18**). The bromohydrin (4*S*)-**20** was treated with K_2CO_3 in MeOH to afford the

Table 1.



Entry	Ag salt (equiv)	Temperature	Time (h)	Products (%)
1	$Ag(CF_3SO_3)$ (2.0)	−20 to 0 °C	1	(±)-**5** (42%)
2	$AgClO_4$ (2.0)	0°C–rt	1	(±)-**5** (38%)
3	$AgClO_4$ (0.8)	0°C–rt	1	(±)-**5** (61%)
4	$Ag(CF_3COO)$ (2.0)	rt	1	(±)-**5**+(±)-**16** (59%)[a]
5	Ag_2CO_3 (2.0)	80 °C	15	(±)-**5** (49%)
6	Ag_2SO_4 (2.0)	80 °C	15	(±)-**5** (32%)
7	$AgNO_3$ (2.0)	rt	21	(±)-**5** (28%)+(±)-**15** (47%)

[a] Yield after conversion of a mixture of (±)-**5** and (±)-**16** into (±)-**5**.



Scheme 4. (a) 80% AcOH aq.; (b) $CBr_4/Ph_3P/CH_2Cl_2$; (c) $^tBuMe_2SiCl$/imidazole/DMF; (d) K_2CO_3/MeOH; (e) $PhCH_2OH/BF_3\cdot Et_2O/CH_2Cl_2$; (f) $AlCl_3$/*m*-xylene/CH_2Cl_2; (g) anisole/$BF_3\cdot Et_2O/CH_2Cl_2$; (h) $AgNO_3$/MS 4 Å/$MeNO_2$; (i) Zn/NH_4OAc/MeOH; (j) (1) OsO_4/*N*-methylmorpholine *N*-oxide/acetone–H_2O, (2) recrystallization; (k) MOM-Cl/diisoproethylpylamine/MeCN; (l) Dibal-H/benzene.

desired (4*S*)-4,5-epoxy-2(*E*)-pentenoate **17** in 85% yield. Optical purity of the present (4*S*)-**17** was estimated to be 93% ee by means of HPLC analysis. Conversion of (4*S*)-**17** into (4*R*)-**17** without loss of optical purity was carried out by modification of the reported procedure.[7] The reaction of (4*S*)-**17** with benzyl alcohol in the presence of $BF_3\cdot Et_2O$ gave (4*R*)-**23** ($[\alpha]_D=-57.0$ ($c=0.52$, $CHCl_3$) corresponding to 93% ee) in 55% yield. Bromination of (4*R*)-**23** provided (4*R*)-**24** ($[\alpha]_D=-40.2$ ($c=0.52$, $CHCl_3$) corresponding to 93% ee; 95% yield)) followed by deprotection of the benzyl group using the $AlCl_3$/*m*-xylene system[7] afforded bromohydrin (4*R*)-**20** ($[\alpha]_D$ −2.50 ($c=0.52$, $CHCl_3$) in 87% yield. An alkaline treatment of (4*R*)-**20** yielded the desired (4*R*)-**17** ($[\alpha]_D=-29.1$ ($c=0.51$, $CHCl_3$) corresponding to 93% ee) in 85% yield. The reaction of (4*R*)-**17** and anisole in the presence of $BF_3\cdot Et_2O$ followed by enzymatic separation gave (4*R*)-**4** ($[\alpha]_D=+2.00$ ($c=0.51$, $CHCl_3$) corresponding to 93% ee; 47% yield) and (4*R*)-**8** ($[\alpha]_D=+17.7$ ($c=0.50$, $CHCl_3$) corresponding to 93% ee; 14% yield). The former (4*R*)-**4** was converted into the bromide (4*R*)-**13** ($[\alpha]_D=+3.00$ ($c=0.5$, $CHCl_3$) in 92% yield in the same way as (±)-**13**. Treatment of (4*R*)-**13** with $AgNO_3$ and MS 4 Å in $MeNO_2$ furnished the nitrate (4*S*)-**15** ($[\alpha]_D=+15.9$ ($c=0.51$, $CHCl_3$); 91% yield) which was converted to the desired (4*S*)-**5** ($[\alpha]_D=+1.00$ ($c=0.5$, $CHCl_3$) corresponding to 93% ee) in 87% yield in the same way as in the case of (±)-**15**. Osmium tetroxide-catalyzed dihydroxylation followed by treatment with *N*-methylmorpholine *N*-oxide gave the 3,4-*anti*-γ-lactone (4*S*)-**25** ($[\alpha]_D=-72.2$ ($c=0.41$, MeOH) corresponding to 93% ee; 78% yield) and the 3,4-*syn*-diastereomer ($[\alpha]_D=-86.0$ ($c=0.11$, MeOH); 2% yield). This high diastereoselectivity (3,4-*anti*: 3,4-*syn*=39:1) was understood by the reported explanation.[8] A transition state D in which the carbon–oxygen bond is near the plane of the conjugated double bond is compatible with the observed stereochemical course of the hydroxylation reaction. Presumably, this conformation results from a favorable interaction between the *p*-orbital of the double bond and an unshared pair on the γ-oxygen. Consequently, osmium tetroxide attacks from the less stereochemically hindered β-side. Recrystallization of the 93% ee of (4*S*)-**25** afforded

the enantiomerically pure (4*S*)-**25**. Treatment of (4*S*)-**25** with chloromethyl methyl ether (MOM-Cl) furnished the di-MOM ether (4*S*)-**26** ($[\alpha]_D=-19.7$ ($c=0.49$, $CHCl_3$); 78% yield). Reduction of (4*S*)-**26** with Dibal-H gave the (4*S*)-diol **7** ($[\alpha]_D=-39.3$ ($c=0.51$, MeOH)) in 81% yield, whose spectral data were identical with those ($[\alpha]_D=-22.7$ ($c=16.21$, MeOH) and ^{1}H NMR) of the reported (4*S*)-**7**.[9] The synthesis of (−)-anisomycin **6** from (4*S*)-**7** is already achieved.[9] From these experiments, conversion of the bromide (4*R*)-**13** into the nitrate (4*S*)-**15** from a stereochemical point of view was found to occur along with complete inversion at the C_4-position. In conclusion, the stereoselective conversion of (4*R*)-5-hydroxy-4-(4′-methoxypheny)-2(*E*)-pentenoate **4** into the (4*S*)-4-hydroxy-5-(4′-methoxyphenyl)-2(*E*)-pentenoate **5** using the $AgNO_3$/MS 4 Å/$MeNO_2$ system was accomplished along with complete inversion at the C_4-position, and the synthesis of the intermediate (4*S*)-**7** for the chiral synthesis of (−)-anisomycin **6** from (4*S*)-**5** based on osmium tetroxide-catalyzed stereoselective hydroxylation was achieved.

4. Experimental

4.1. General

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded by a JEOL EX 400 spectrometer (Tokyo, Japan). Spectra were taken with 5–10% (w/v) solution in $CDCl_3$ with Me_4Si as an internal reference. High-resolution mass spectra (HRMS) and the fast atom bombardment mass spectra (FAB MS) were obtained with a JEOL JMS-DX 303 (matrix; glycerol, *m*-nitrobenzyl alcohol) spectrometer. IR spectra were recorded on a JASCO FT/IR-300 spectrometer. The HPLC system was composed of a detector (UV detector SSC-5200, Senshu), pump (SSC-3210, Senshu) and integrator (chromatocorder SIC 21). HPLC analysis conditions were as follows; column: CHIRALCEL AS, eluent: *n*-hexane/EtOH=100:1, Detection: UV at 254 nm, Flow rate; 1 mL/min. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

4.1.1. (±) Methyl 4-(4′-methoxyphenyl)-5-tosyloxy-2(*E*)-pentenoate 9. A mixture of (±)-**4** (2.774 g, 11.7 mmol), *p*-toluenesulfonic anhydride (Ts_2O, 4.60 g, 14.1 mmol), pyridine (1.40 g, 17.7 mmol) in benzene (25 mL) was stirred for 2 d at 50 °C. The generated precipitate was filtered off with the aid of celite and the filtrate was washed with 1 M aqueous HCl and 7% aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (80 g, *n*-hexane/AcOEt=5:1) to afford (±)-**9** (4.393 g, 96%) as a colorless oil. (±)-**9**: IR (neat): 1722 cm^{-1}; ^{1}H NMR: δ 2.44 (3H, s), 3.71 (3H, s), 3.76 (1H, br.q, $J=8$ Hz), 3.79 (3H, s), 4.20 (2H, d, $J=7$ Hz), 5.79 (1H, dd, $J=2$, 16 Hz), 6.81 (2H, d, $J=8$ Hz), 6.97 (1H, dd, $J=8$, 16 Hz), 7.00 (2H, d, $J=8$ Hz), 7.30 (2H, d, $J=8$ Hz), 7.70 (2H, d, $J=8$ Hz). Anal. Calcd for $C_{20}H_{22}SO_6$: C, 61.52; H, 5.68. Found: C, 61.32; H, 5.56. MS (FAB) *m*/*z*: 391 ($M^+ +1$).

4.1.2. (±) Methyl 4-(2′-methoxyphenyl)-5-tosyloxy-2(*E*)-pentenoate 10. A mixture of (±)-**8** (1.042 g, 4.41 mmol), *p*-toluenesulfonic anhydride (Ts_2O, 1.73 g, 5.3 mmol), pyridine (2 mL) in benzene (15 mL) was stirred for 3 d at 50 °C. The reaction mixture was worked up in the same way for (±)-**9** to afford (±)-**10** (1.38 g, 80%) as a colorless oil. (±)-**9**: IR (neat): 1722 cm^{-1}; ^{1}H NMR: δ 2.44 (3H, s), 3.71 (3H, s), 3.73 (3H, s), 4.16 (1H, q, $J=10$ Hz), 4.26 (1H, dd, $J=6$, 10 Hz), 4.30 (1H, dd, $J=7$, 10 Hz), 5.80 (1H, dd, $J=2$, 16 Hz), 6.81 (1H, d, $J=8$ Hz), 6.87 (1H, t, $J=8$ Hz), 7.00 (1H, dd, $J=2$, 8 Hz), 7.02 (1H, dd, $J=8$, 16 Hz), 7.23 (1H, dt, $J=2$, 8 Hz), 7.295 (2H, d, $J=8$ Hz), 7.69 (2H, d, $J=9$ Hz). Anal. Calcd for $C_{20}H_{22}SO_6$: C, 61.52; H, 5.68. Found: C, 61.09; H, 5.87. MS (FAB) *m*/*z*: 391 ($M^+ +1$).

4.1.3. Solvolysis of (±)-9. A solution of (±)-**9** (0.500 g, 1.28 mmol) in water-saturated nitromethane (50 mL) was stirred for 2 d at 90 °C. The reaction mixture was diluted with water and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue. A suspension of the above-mentioned residue and lipase OF-360 from Candida rugosa (0.20 g) in phosphate buffer (pH 7.4, 150 mL) was stirred for 3 d at 33 °C. The reaction mixture was extracted with ether and the organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (20 g, *n*-hexane/AcOEt=5:1) to afford (±)-**9** (0.170 g, 34% recovery). On the other hand, the water layer was acidified with 1 M aqueous HCl and extracted with ether. Evaporation of the organic solvent gave a residue (±)-**11**, which was treated with CH_2N_2–ether solution to afford an oil. It was chromatographed on silica gel (20 g, *n*-hexane/AcOEt=5:1) to afford (±)-**5** (0.153 g, 51%) as a colorless oil. (±)-**5**: IR (neat): 3456, 1722 cm^{-1}; ^{1}H NMR: δ 2.12 (1H, br.s), 2.73 (1H, dd, $J=8$, 14 Hz), 2.88 (1H, dd, $J=5$, 14 Hz), 3.73 (3H, s), 3.78 (3H, s), 4.47 (1H, dq, $J=2$, 5 Hz), 6.05 (1H, dd, $J=2$, 16 Hz), 6.85 (2H, d, $J=8$ Hz), 6.99 (1H, dd, $J=5$, 16 Hz), 7.13 (2H, d, $J=8$ Hz). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.95; H, 6.85. MS (FAB) *m*/*z*: 237 ($M^+ +1$).

4.1.4. Solvolysis of (±)-10. A solution of (±)-**10** (0.251 g, 0.64 mmol) in water-saturated nitromethane (40 mL) was stirred for 4 d at 90 °C. The reaction mixture was diluted with water and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was treated with CH_2N_2–ether solution to afford an oil. It was chromatographed on silica gel (20 g, *n*-hexane/AcOEt=5:1) to afford (±)-**12** (0.081 g, 53%) as a colorless oil. (±)-**12**: IR (neat): 3451, 1717 cm^{-1}; ^{1}H NMR: δ 2.49 (1H, br.s), 2.82 (1H, dd, $J=8$, 14 Hz), 3.01 (1H, dd, $J=5$, 14 Hz), 3.73 (3H, s), 3.84 (3H, s), 4.56 (1H, ddt, $J=2$, 5, 5 Hz), 6.06 (1H, dd, $J=2$, 16 Hz), 6.88 (1H, br.d, $J=9$ Hz), 6.92 (1H, t, $J=8$ Hz), 7.02 (1H, dd, $J=5$, 16 Hz), 7.13 (1H, dd, $J=2$, 8 Hz), 7.24 (1H, t, $J=8$ Hz). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.67; H, 6.80. MS (FAB) *m*/*z*: 237 ($M^+ +1$).

4.1.5. (±) Methyl-5-bromo-4-(4′-methoxyphenyl)-2(*E*)-pentenoate 13. To a solution of (±)-**4** (2.012 g, 8.52 mmol) in MeCN (40 mL) were added triphenyl phosphine (Ph_3P; 10.06 g, 38.4 mmol) and *N*-bromosuccinimide (NBS; 6.83 g, 38.3 mmol) at 0 °C and the reaction mixture was

stirred for 2 h at room temperature. The reaction mixture was diluted with water and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (80 g, *n*-hexane/AcOEt=5:1) to afford (±)-**13** (2.104 g, 83%) as a colorless oil. (±)-**13**: IR (neat): 1723 cm^{-1}; ^1H NMR: δ 3.60 (2H, dd, J=2, 7 Hz), 3.73 (3H, s), 3.79 (3H, s), 3.80 (1H, br.q, J=7 Hz), 5.88 (1H, dd, J=2, 16 Hz), 6.88 (2H, d, J=9 Hz), 7.09 (1H, dd, J=8, 16 Hz), 7.11 (2H, d, J=9 Hz). Anal. Calcd for $C_{13}H_{15}BrO_3$: C, 52.19; H, 5.05. Found: C, 52.48; H, 4.64. MS (FAB) *m/z*: 299, 301 ($M^+ + 1$).

4.1.6. Solvolysis of (±)-13. A solution of (±)-**13** (0.500 g, 1.67 mmol) in water-saturated nitromethane (20 mL) was stirred for 12 h at 80 °C. The reaction mixture was diluted with water and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (20 g) to afford a mixture (0.382 g) of (±)-**13** and (±)-**14** from *n*-hexane/AcOEt=10:1eluent and (±)-**5** (0.024 g, 6%) from *n*-hexane/AcOEt=5:1eluent. To a solution of this mixture (0.382 g) in $MeNO_2$ (10 mL) were added molecular sieves (4 Å; 0.5 g) and silver nitrate ($AgNO_3$; 0.43 g, 2.53 mmol) and the whole mixture was stirred for 12 h at room temperature. The generated precipitate was filtered off with the aid of celite and the filtrate was diluted with water and ether. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (20 g, *n*-hexane/AcOEt=30:1) to afford (±)-**15** (0.298 g, 63% overall yield) as a colorless oil. (±)-**15**: IR (neat): 1726 cm^{-1}; ^1H NMR: 2.93 (1H, dd, J=6, 14 Hz), 3.03 (1H, dd, J=7, 15 Hz), 3.75 (3H, s), 3.79 (3H, s), 5.58 (1H, dq, J=2, 6 Hz), 6.01 (1H, dd, J=2, 16 Hz), 6.84 (1H, dd, J=6, 16 Hz), 6.85 (2H, d, J=8 Hz), 7.12 (2H, d, J=8 Hz). Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.77; H, 5.32; N, 5.02. MS (FAB) *m/z*: 281 (M^+).

4.1.7. Solvolysis of (±)-13 (Table 1).

1) To a solution of (±)-**13** (0.400 g, 1.33 mmol) in water-saturated nitromethane (10 mL) was added silver trifrate ($Ag(CF_3SO_3)$; 0.683 g, 2.66 mmol) and the whole mixture was stirred for 1 h at 0 °C. The generated precipitate was filtered off with the aid of celite and the filtrate was diluted with water and ether. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt=15:1) to afford (±)-**5** (0.132 g, 42%).
2) To a solution of (±)-**13** (0.403 g, 1.34 mmol) in water-saturated nitromethane (10 mL) was added silver perchlorate ($AgClO_4$; 0.555 g, 2.68 mmol) and the whole mixture was stirred for 1 h at 0 °C. The reaction mixture was worked up in the same way as 1) to afford (±)-**5** (0.119 g, 38%).
3) To a solution of (±)-**13** (0.400 g, 1.33 mmol) in water-saturated nitromethane (10 mL) was added silver perchlorate ($AgClO_4$; 0.220 g, 1.06 mmol) and the whole mixture was stirred for 1 h at 0 °C. The reaction mixture was worked up in the same way as 1) to afford (±)-**5** (0.193 g, 61%).
4) To a solution of (±)-**13** (0.401 g, 1.34 mmol) in water-saturated nitromethane (10 mL) was added silver trifluoroacetate ($Ag(CF_3COO)$; 0.592 g, 2.68 mmol) and the whole mixture was stirred for 1 h at room temperature. The reaction mixture was worked up in the same way as 1) to afford a mixture (0.42 g) of (±)-**5** and (±)-**16**. To a solution of the above mixture in MeOH (8 mL) was added K_2CO_3 (90 mg) and the whole mixture was stirred for 1.5 h at room temperature. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt=15:1) to afford (±)-**5** (0.188 g, 59%).
5) To a solution of (±)-**13** (0.401 g, 1.34 mmol) in water-saturated nitromethane (10 mL) was added silver carbonate (Ag_2CO_3; 0.739 g, 2.68 mmol) and the whole mixture was stirred for 15 h at 80 °C. The reaction mixture was worked up in the same way as 1) to afford (±)-**5** (0.155 g, 49%).
6) To a solution of (±)-**13** (0.401 g, 1.34 mmol) in water-saturated nitromethane (10 mL) was added silver sulfate (Ag_2SO_4; 0.835 g, 2.68 mmol) and the whole mixture was stirred for 15 h at 80 °C. The reaction mixture was worked up in the same way as 1) to afford (±)-**5** (0.100 g, 32%).
7) To a solution of (±)-**13** (0.400 g, 1.33 mmol) in water-saturated nitromethane (10 mL) was added silver nitrate ($AgNO_3$; 0.451 g, 2.66 mmol) and the whole mixture was stirred for 21 h at room temperature. The reaction mixture was worked up in the same way as 1) to afford (±)-**15** (0.175 g, 47%) and (±)-**5** (0.087 g, 28%).

4.1.8. Synthesis of (±) methyl-4-hydroxy-5-(4′-methoxyphenyl)-2(*E*)-pentenoate 5 from (±)-13 via (±)-15. To a solution of (±)-**13** (1.43 g, 4.78 mmol) in nitromethane (20 mL) were added molecular sieves (4 Å; 2.0 g) and silver nitrate ($AgNO_3$; 1.62 g, 9.54 mmol) and the whole mixture covered with aluminum foil was stirred for 4 h at room temperature. The reaction mixture was worked up in the same way as the previous (±)-**15** to give (±)-**15** (1.222 g, 91%). To a mixture of Zn-dust (0.7 g) and CH_3COONH_4 (0.5 g) in MeOH (5 mL) was added a solution of (±)-**15** (0.501 g, 1.78 mmol) in MeOH (5 mL) and the whole mixture was stirred for 1 h at 0 °C. After the generated precipitate was filtered off with the aid of celite, the filtrate was diluted with water and ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (20 g, *n*-hexane/AcOEt=5:1) to afford (±)-**5** (0.371 g, 88%) as a colorless oil. The NMR data of the present (±)-**5** were identical with those of the previous (±)-**5**.

4.1.9. Methyl (4*S*)-(4,5)-epoxy-2(*E*)-pentenoate 17. (1) A solution of commercially available (4*S*)-**18** (31.19 g, 0.17 mol) in 80% aqueous AcOH (200 mL) was stirred for 30 min at 80 °C. The reaction mixture was diluted with toluene and condensed under reduced pressure to give a crude diol (4*S*)-**19** (25.21 g, quantitative yield). (2) To a solution of (4*S*)-**19** (25.21 g) in CH_2Cl_2 (120 mL) were added Ph_3P (16.92 g, 0.0645 mol) and carbon tetrabromide

(CBr_4; 21.39 g, 0.0645 mol) and the whole mixture was refluxed for 1 h with stirring. The reaction mixture was evaporated to afford a residue, which was chromatographed on silica gel (150 g, *n*-hexane/AcOEt=10:1) to provide an inseparable mixture (18.81 g) of (4*S*)-**20** and (4*R*)-**21**. (3) To a solution of the above-mentioned mixture (18.81 g) in DMF (120 mL) were added imidazole (18.38 g, 0.270 mol) and *tert*-butyldimethylsilyl chloride (TBDMSCl; 5.42 g, 0.034 mol) at 0 °C and the whole mixture was stirred for 2 h at 0 °C. The reaction mixture was diluted with brine and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to provide a residue, which was chromatographed on silica gel (200 g) to afford an oily (4*R*)-**22** (8.25 g, 15% overall yield from (4*S*)-**18**) from *n*-hexane/AcOEt=20:1 elute and an oily (4*S*)-**20** (11.11 g, 32% overall yield from (4*S*)-**18**) from *n*-hexane/AcOEt=5:1 elute, respectively. (4*S*)-**20**: IR (neat): 3451, 1716 cm^{-1}; ^1H NMR: δ 2.72 (1H, d, J=7 Hz), 3.42 (1H, dd, J=7, 11 Hz), 3.57 (1H, dd, J=4, 11 Hz), 3.76 (3H, s), 4.51–4.58 (1H, m), 6.16 (1H, dd, J=2, 16 Hz), 6.88 (1H, dd, J=5, 16 Hz). MS (FAB) *m*/*z*: 209.211 (M^++1). (4*R*)-**22**: IR (neat): 1725 cm^{-1}; ^1H NMR: δ 0.06 (3H, s), 0.07 (3H, s), 0.88 (9H, s), 3.75 (3H, s), 3.83 (1H, dd, J=7, 11 Hz), 3.93 (1H, dd, J=5, 11 Hz),4.47–4.53 (1H, m), 6.02 (1H, dd, J=1, 15 Hz), 6.93 (1H, dd, J=9, 15 Hz). MS (FAB) *m*/*z*: 323.325 (M^++1). (4) A mixture of molecular sieves (3 Å; 7.5 g) and K_2CO_3 (17.1 g, 0.124 mol) in MeOH (450 mL) was stirred for 30 min at 0 °C, and (4*S*)-**20** (14.42 g, 0.069 mol) in MeOH (50 mL) was slowly added to the above-mentioned mixture. The reaction mixture was stirred for 2.5 h at 0 °C and filtered with the aid of filter paper. The MeOH was distilled under ordinary pressure and the residue was chromatographed on silica gel (200 g, *n*-hexane/AcOEt=20:1) to afford (4*S*)-**17** (7.51 g, 85%) as a colorless oil. (4*S*)-**17**: $[\alpha]_D^{24}=+22.3$ (c=0.51, $CHCl_3$) corresponding to 93% ee by means of HPLC analysis). (4*R*)-**17**: t_R=17.1 min, (4*S*)-**17**: t_R=20.0 min. The NMR data of (4*S*)-**17** were identical with those of the reported (±)-**17**.[4b]

4.1.10. Methyl (4*R*)-(4,5)-epoxy-2(*E*)-pentenoate 17. (1) To a solution of (4*S*)-**17** (7.62 g, 0.0595 mol) in CH_2Cl_2 (80 mL) were added benzyl alcohol ($PhCH_2OH$; 32.12 g, 0.298 mol) and $BF_3\cdot Et_2O$ (8 mL, 0.064 mol) at −20 °C and the whole mixture was stirred for 1.5 h at 0 °C. The reaction mixture was diluted with brine and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to provide a residue, which was chromatographed on silica gel (200 g, *n*-hexane/AcOEt=5:1) to afford (4*R*)-**23** (7.794 g, 56%) as a colorless oil. (4*R*)-**23**: $[\alpha]_D^{23}=-57.0$ (c=0.52, $CHCl_3$) corresponding to 93% ee): IR (neat): 3433, 1721 cm^{-1}; ^1H NMR: δ 3.65 (1H, dd, J=8, 12 Hz), 3.73 (1H, br.dd, J=5, 12 Hz), 3.81 (3H, s), 4.16–4.21 (1H, m), 4.49 (1H, d, J=12 Hz), 4.71 (1H, d, J=12 Hz), 6.18 (1H, dd, J=2, 16 Hz), 6.92 (1H, dd, J=6, 16 Hz), 7.32–7.44 (5H, m). MS (FAB) Calcd For $C_{13}H_{16}O_4$ *m*/*z*: 237.1127 (M^++1). Found *m*/*z*: 237.1154. (2) To a solution of (4*R*)-**23** (3.00 g, 12.7 mmol) in CH_2Cl_2 (50 mL) were added Ph_3P (6.66 g, 25.4 mmol) and carbon tetrabromide (CBr_4; 8.42 g, 25.4 mmol) at 0 °C and the whole mixture was stirred for 1 h at room temperature. The reaction mixture was evaporated to afford a residue, which was chromatographed on silica gel (150 g, *n*-hexane/AcOEt=20:1) to provide (4*R*)-**24** (3.596 g, 95%) as a colorless oil. (4*R*)-**24**: $[\alpha]_D^{24}=-40.2$ (c=0.52, $CHCl_3$) corresponding to 93% ee); IR (neat): 1722 cm^{-1}; ^1H NMR: δ 3.41 (1H, dd, J=7, 12 Hz), 3.46 (1H, dd, J=7, 12 Hz), 3.77 (3H, s), 4.21 (1H, dq, J=2, 7 Hz), 4.50 (1H, d, J=12 Hz), 4.63 (1H, d, J=12 Hz), 6.13 (1H, dd, J=2, 15 Hz), 6.86 (1H, dd, J=7, 15 Hz), 7.28–7.40 (5H, m). Anal. Calcd for $C_{13}H_{15}BrO_3$: C, 52.19; H, 5.05. Found: C, 51.65; H, 4.88. MS (FAB) *m*/*z*: 299.301 (M^++1). (3) To a suspension of $AlCl_3$ (8.92 g, 66.9 mmol) in CH_2Cl_2 (120 mL) was added a solution of (4*R*)-**24** (10.167 g, 34 mmol) in *m*-xylene (25 mL) at −20 °C and the whole mixture was stirred for 30 min at the same temperature. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to provide a residue, which was chromatographed on silica gel (200 g, *n*-hexane/AcOEt=5:1) to afford (4*R*)-**20** (6.170 g, 87%) as a colorless oil. (4*R*)-**20**: $[\alpha]_D^{23}=-2.50$ (c=0.52, $CHCl_3$) corresponding to 93% ee. The spectral data (IR and NMR) of (4*R*)-**20** were identical with those of (4*S*)-**20**. (4) A mixture of molecular sieves (3 Å; 3.0 g) and K_2CO_3 (8.98 g, 65 mmol) in MeOH (350 mL) was stirred for 30 min at 0 °C, and (4*R*)-**20** (13.59 g, 65 mmol) in MeOH (50 mL) was slowly added to the above-mentioned mixture. The reaction mixture was stirred for 30 min at 0 °C and filtered with the aid of filter paper. The MeOH was distilled under ordinary pressure and the residue was chromatographed on silica gel (200 g, *n*-hexane/AcOEt=20:1) to afford (4*R*)-**17** (7.101 g, 85%) as a colorless oil. (4*R*)-**17**: $[\alpha]_D^{24}=-29.1$ (c=0.51, $CHCl_3$) corresponding to 93% ee by means of HPLC analysis), HPLC analysis conditions were the same as for (4*S*)-**17**. The NMR data of (4*R*)-**17** were identical with those of the reported (±)-**17**.[4b]

4.1.11. Methyl (4*R*)-5-hydroxy-4-(4′-methoxyphenyl)-2(*E*)-pentenoate 4. (1) To a solution of (4*R*)-**17** (3.71 g, 28.9 mmol) in CH_2Cl_2 (50 mL) were added anisole (PhOMe; 9.39 g, 86.8 mmol) and $BF_3\cdot Et_2O$ (7 mL, 56 mmol) at −20 °C and the whole mixture was stirred for 1 h at −20 °C. The reaction mixture was diluted with brine and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to provide a residue, which was chromatographed on silica gel (100 g) to afford (4*R*)-**8** (0.375 g, 5% yield) from *n*-hexane/AcOEt=3:1 elute, and 1:3 mixture (2.620 g) of (4*R*)-**8** and (4*R*)-**4** from *n*-hexane/AcOEt=3:1 elute, and (4*R*)-**4** (1.504 g, 22% yield) from *n*-hexane/AcOEt=2:1 elute, respectively. (2) To a solution of a 1:3 mixture (2.620 g) of (4*R*)-**8** and (4*R*)-**4** in pyridine (5 mL) was added Ac_2O (2.26 g, 22.1 mmol) and the whole mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with brine and extracted with ether. The organic layer was washed with 2 M aqueous HCl, and 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (60 g, *n*-hexane/AcOEt=10:1) to afford a mixture of the corresponding acetates (2.81 g). (3) A suspension of the above-mentioned mixture (2.81 g) and lipase Amano P from *Pseudomonas* sp. (0.50 g) in phosphate buffer (pH 7.4; 300 mL) was stirred at 33 °C for 12 h. The reaction mixture was filtered, and the precipitate was washed with ether. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (60 g) to give an acetate

(0.707 g, 9% yield from (4*R*)-**17**)) of (4*R*)-**8** from *n*-hexane/AcOEt=7:1 elute and (4*R*)-**4** (1.737 g, total; 3.241 g (47% overall yield from (4*R*)-**17**)) as a homogeneous oil from *n*-hexane/AcOEt=2:1 elute, respectively. (4*R*)-**4**: $[\alpha]_D^{24}=+2.00$ ($c=0.51$, $CHCl_3$) corresponding to 93% ee by means of HPLC analysis), The NMR data of (4*R*)-**4** were identical with those of the reported (±)-**4**.[5] Acetate of (4*R*)-**8**: $[\alpha]_D^{26}=+8.98$ ($c=0.50$, $CHCl_3$) corresponding to 93% ee by means of HPLC analysis): IR (neat): 1740 cm^{-1}; ^1H NMR: δ 2.02 (3H, s), 3.72 (3H, s), 3.82 (3H, s), 4.23 (1H, br, q, $J=7.0$ Hz), 4.33 (1H, dd, $J=11.0$, 5.0 Hz), 4.40 (1H, dd, $J=11.0$, 9.0 Hz), 5.87 (1H, dd, $J=16.0$, 2.0 Hz), 6.88 (1H, dd, $J=8.0$, 2.0 Hz), 6.92 (1H, dt, $J=8.0$, 2.0 Hz), 7.11 (1H, dd, $J=8.0$, 2.0 Hz), 7.16 (1H, dd, $J=16.0$, 7.0 Hz), 7.25 (1H, dt, $J=8.0$, 2.0 Hz). FAB MS *m/z*: 279 $(M+1)^+$; Anal. Found: C, 64.60; H, 6.50. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52%.

4.1.12. Methyl (4*S*)-4-hydroxy-5-(4′-methoxyphenyl)-2(*E*)-pentenoate 5. (1) To a solution of (4*R*)-**4** (2.01 g, 8.51 mmol) in CH_2Cl_2 (40 mL) were added triphenyl phosphine (Ph_3P; 4.46 g, 17 mmol) and carbon tetrabromide (CBr_4; 8.46 g, 25.5 mmol) at 0 °C and the whole mixture was stirred for 1.5 h at room temperature. The reaction mixture was evaporated to afford a residue, which was chromatographed on silica gel (80 g, *n*-hexane/AcOEt=30:1) to provide (4*R*)-**13** (2.342 g, 92%) as a colorless oil. (4*R*)-**13**: $[\alpha]_D^{27}=+3.00$ ($c=0.50$, $CHCl_3$) corresponding to 93% ee by means of HPLC analysis), The NMR data of (4*R*)-**13** were identical with those of the reported (±)-**13**. (2) To a solution of (4*R*)-**13** (1.43 g, 4.8 mmol) in nitromethane (20 mL) were added molecular sieves (4 Å; 2.0 g) and silver nitrate ($AgNO_3$; 1.62 g, 9.54 mmol) and the whole mixture covered with aluminum foil was stirred for 24 h at room temperature. The reaction mixture was worked up in the same way as the previous (±)-**15** to give (4*S*)-**15** (1.22 g, 91%). (4*S*)-**15**: $[\alpha]_D^{27}=+15.9$ ($c=0.51$, $CHCl_3$) corresponding to 93% ee by means of HPLC analysis), The NMR data of (4*S*)-**15** were identical with those of the reported (±)-**15**. (3) To a mixture of Zn-dust (1.14 g) and CH_3COONH_4 (1.14 g) in MeOH (5 mL) was added a solution of (4*S*)-**15** (1.140 g, 4.06 mmol) in MeOH (7 mL) and the whole mixture was stirred for 1 h at 0 °C. The generated precipitate was filtered off with the aid of celite and the filtrate was diluted with water and ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (40 g, *n*-hexane/AcOEt=5:1) to afford (4*S*)-**5** (0.833 g, 87%) as a colorless oil. (4*S*)-**5**: $[\alpha]_D^{26}=+1.00$ ($c=0.50$, $CHCl_3$) corresponding to 93% ee by means of HPLC analysis), The NMR data of (4*S*)-**5** were identical with those of the previous (±)-**5**.

4.1.13. (2*S*,3*S*,4*S*)-4-Hydroxy-2,3-dimethoxymethyl-5-(4′-methoxyphenyl)-pentanol 7. (1) To a solution of 50% aqueous *N*-methylmorpholine *N*-oxide (0.58 mL, 2.49 mmol) and 2% aqueous osmium tetraoxide (OsO_4; 3.16 mL, 10 mol%) in acetone (5 mL) was added a solution of (4*S*)-**5** (0.588 g, 2.49 mmol) in acetone (5 mL) at 0 °C and the whole mixture was stirred for 2 h at the same temperature. The reaction mixture was diluted with 10% aqueous Na_2SO_3 (5 mL) at 0 °C and the whole mixture was stirred for 30 min. The generated precipitate was filtered with the aid of celite and the filtrate was condensed. The residue was diluted with ether and treated with 10% aqueous HCl. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (30 g, *n*-hexane/AcOEt=1:1) to afford diastereomeric lactone (2*S*,3*R*,4*S*)-**25** (0.010 g, 2%) and the desired (2*R*,3*S*,4*S*)-**25** (0.463 g, 78%) in elution order. Crystallization of (2*R*,3*S*,4*S*)-**25** from $CHCl_3$ gave a colorless crystal. (2*R*,3*S*,4*S*)-**25**: mp 81–82 °C, $[\alpha]_D^{24}=-72.2$ ($c=0.41$, MeOH) corresponding to >99% ee by means of HPLC analysis): IR (KBr): 3298, 1756 cm^{-1}; ^1H NMR: δ 2.82 (1H, dd, $J=8$, 15 Hz), 3.13 (1H, dd, $J=3$, 15 Hz), 3.74 (3H, s), 3.88 (1H, t, $J=9$ Hz), 4.25 (1H, dt, $J=3$, 8 Hz), 4.30 (1H, d, $J=9$ Hz), 6.84 (2H, d, $J=9$ Hz), 7.17 (2H, d, $J=9$ Hz). Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 50.90; H, 5.90. MS (FAB) *m/z*: 239 (M^++1). (2*S*,3*R*,4*S*)-**25**: $[\alpha]_D^{22}=-86.0$ ($c=0.11$, MeOH) corresponding to 93% ee by means of HPLC analysis): IR (KBr): 3429, 1758 cm^{-1}; ^1H NMR: δ 2.90 (1H, dd, $J=8$, 15 Hz), 3.08 (1H, dd, $J=5$, 15 Hz), 3.76 (3H, s), 4.03 (1H, d, $J=5$ Hz), 4.19 (1H, t, $J=5$ Hz), 4.72 (1H, dt, $J=5$, 8 Hz), 6.84 (2H, d, $J=9$ Hz), 7.20 (2H, d, $J=9$ Hz). Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.37; H, 5.91. MS (FAB) *m/z*: 239 (M^++1). (2) To a solution of (2*R*,3*S*,4*S*)-**25** (0.101 g, 0.42 mmol) and *N*,*N*-diisopropylethylamine (1.32 g, 9.29 mmol) in MeCN (1 mL) was added chloromethylmethyl ether (CH_3OCH_2Cl; 0.68 g, 8.45 mmol) at 0 °C and the whole mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with brine and ether at 0 °C, the organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt=8:1) to afford (2*R*,3*S*,4*S*)-**26** (0.107 g, 78%) as a colorless oil. (2*R*,3*S*,4*S*)-**26**: $[\alpha]_D^{24}=-18.7$ ($c=0.49$, $CHCl_3$) corresponding to >99% ee by means of HPLC analysis): IR (neat): 1790 cm^{-1}; ^1H NMR: δ 2.94 (1H, dd, $J=7$, 14 Hz), 3.15 (1H, dd, $J=4$, 14 Hz), 3.40 (3H, s), 3.44 (3H, s), 3.79 (3H, s), 4.07 (1H, t, $J=7$ Hz), 4.42 (1H, dt, $J=4$, 7 Hz), 4.47 (1H, d, $J=7$ Hz), 4.65 (1H, d, $J=7$ Hz), 4.73 (1H, d, $J=7$ Hz), 4.79 (1H, d, $J=7$ Hz), 5.02 (1H, d, $J=7$ Hz), 6.85 (2H, d, $J=8$ Hz), 7.18 (2H, d, $J=8$ Hz). Anal. Calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.80. Found: C, 58.96; H, 6.97. MS (FAB) *m/z*: 326 (M^+). (3) To a solution of (2*R*,3*S*,4*S*)-**26** (0.076 g, 0.23 mmol) in benzene (5 mL) was added 1 M diisobutylaluminum hydride (Dibal-H) in toluene solution (1.41 mL, 1.41 mmol) at 0 °C and the whole mixture was stirred for 1 h at 0 °C. The reaction mixture was diluted with brine and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt=1:1) to afford (4*S*)-**7** (0.062 g, 81%) as a colorless oil. (4*S*)-**7**: $[\alpha]_D^{24}=-39.3$ ($c=0.51$, MeOH) corresponding to >99% ee by means of HPLC analysis): IR (neat): 3439 cm^{-1}; ^1H NMR: δ 2.62 (1H, dd, $J=10$, 14 Hz), 2.92 (1H, d, $J=5$ Hz), 3.00 (1H, dd, $J=3$, 14 Hz), 3.21 (1H, t, $J=6$ Hz), 3.41 (3H, s), 3.46 (3H, s), 3.65 (1H, dd, $J=4$, 7 Hz), 3.74–3.78 (2H, m), 3.79 (3H, s), 3.91–3.97 (2H, m), 4.71–4.77 (4H, m), 6.85 (2H, d, $J=9$ Hz), 7.18 (2H, d, $J=9$ Hz). Anal. Calcd for $C_{16}H_{26}O_7$: C, 58.17; H, 7.93. Found: C, 57.75; H, 8.06. MS (FAB) *m/z*: 369 (M^++K).

References and notes

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