Synthesis of γ- and δ-Lactone Natural Products by Employing a *trans–cis* Isomerization/Lactonization Strategy

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Alkaline hydrolysis of 4-hydroxy- or/and 5-hydroxy-(2*E*)-alkenoate followed by acid treatment gave the corresponding (2*E*)-alkenoic acids which were subjected to lactone formation reaction without further purification. The crude acids were treated with 2,4,6-trichlorobenzoyl chloride in pyridine to afford γ-lactone or δ-lactone, respectively, accompanied by *trans–cis* isomerization. By this procedure, (±)-(4,5)-*trans*-5-benzyloxy-2-hexen-4-olide (90% overall yield), (*S*)-5-hydroxy-2-penten-4-olide (86% overall yield), (4*S*,5*R*)-5-hydroxy-2-hexen-4-olide (86% overall yield), (4*R*,5*S*)-5-hydroxy-2-hexen-4-olide (82% overall yield), (*S*)-parasorbic acid (58% overall yield) and natural product, (5*R*,7*S*)-7-hydroxy-2-octen-5-olide (euscapholide: 20% overall yield) were synthesized.

Key words lactone formation; *trans–cis* isomerization; euscapholide

The α,β-unsaturated lactones are found as structural subunits in a wide variety of natural products possessing diverse biological activities as shown in Chart 1. Furthermore, simple lactones have been used as intermediates for the synthesis of biologically active compounds. The structure of typical natural products such as (*S*)-parasorbic acid (**1**), (4*R*,5*S*)-osmundalactone (**2**), (4*R*,5*S*)-5-hydroxy-2-hexen-4-olide (**3**), (5*R*,7*S*)-euscapholide (**4**), (+)-asperlin (**5**), (+)-anamarine (**6**), (−)-tarchonanthuslactone (**7**), and fostriecin (**8**) are shown in Chart 1.

In general, the syntheses of α,β-unsaturated lactones are achieved based on the direct lactonization of the corresponding 4- or 5-hydroxy-(2*Z*)-unsaturated esters. To achieve efficient syntheses of α,β-unsaturated lactones, it is necessary to obtain the *Z*-isomer of the α,β-unsaturated esters in a stereoselective manner. This problem could be overcome by applying the modified Horner–Emmons reaction[1] Ring-closing metatheses using Grubbs reagent have recently been reported to be a useful method to construct α,β-unsaturated lactone structures.[2]

We previously reported the syntheses of (4*S*,5*R*)- and (4*R*,5*S*)-4-benzyloxy-5-hydroxy-(2*E*)-hexenoates (**11**) based on a chemoenzymatic method from methyl sorbate (**9**).[3] Hydrolysis of (4*S*,5*R*)- and (4*R*,5*S*)-**11** gave the corresponding 5-hydroxy-(2*E*)-unsaturated carboxylic acids, which were converted to osmundalactones (4*S*,5*R*)- and (4*R*,5*S*)-**2** *via* the formation of δ-lactones (4*S*,5*R*)- and (4*R*,5*S*)-**12** accompanied by *trans–cis* isomerization, respectively as shown in Chart 2. In this paper, a reaction mechanism of isomerization from *E*-isomer to *Z*-isomer is described.[4]

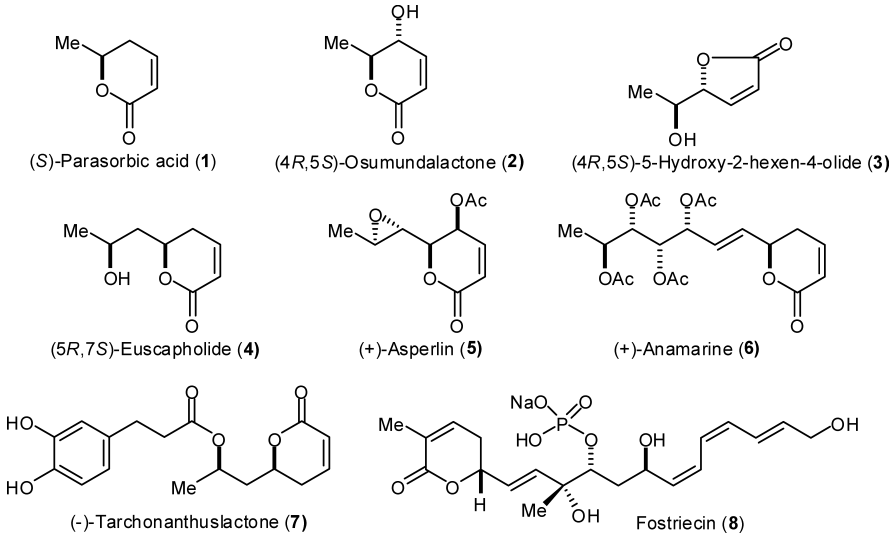

Chart 1

The authors declare no conflict of interest.

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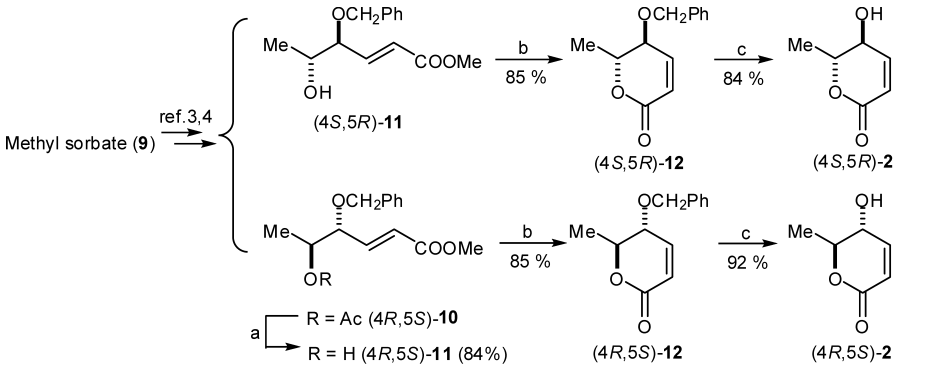
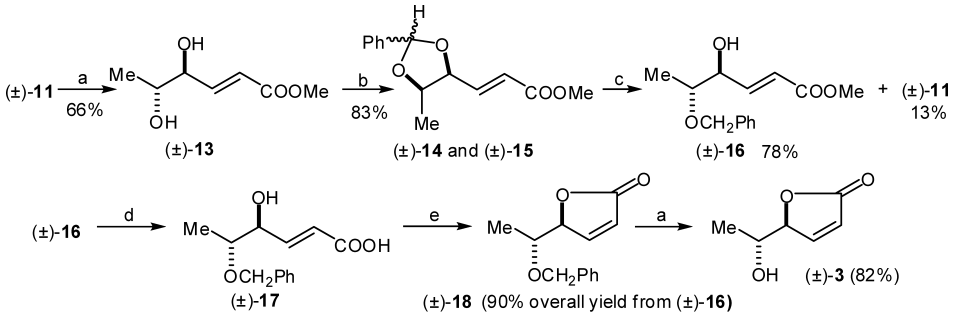


Reagents: a; MeONa / MeOH b; 1) 2M NaOH / *i*-PrOH 2) 2M HCl 3) 2,4,6-trichlorobenzoyl chloride / pyridine
c; $AlCl_3$ / *m*-xylene, CH_2Cl_2

Chart 2



Reagents: a; $AlCl_3$ / *m*-xylene, CH_2Cl_2 b; PhCHO / *p*-TsOH / PhH c; $NaBH_3(CN)$ /$TiCl_4$ / MeCN
d; 1) 2M NaOH / *i*-PrOH 2) 2M HCl e; 2,4,6-trichlorobenzoyl chloride / pyridine

Chart 3

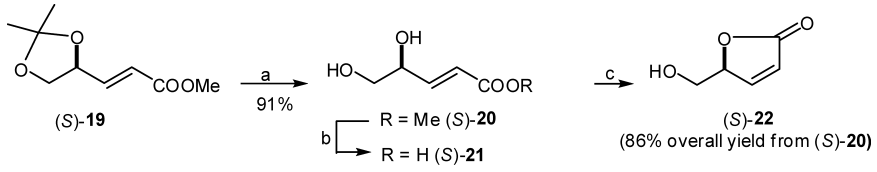
We now report the scope and limitation of the synthesis of *α*,*β*-unsaturated lactone using the above mentioned lactone formation method accompanied by *trans–cis* isomerization from 4- or/and 5-hydroxy-2(*E*)-unsaturated ester and application to the first synthesis of (5*R*,7*S*)-euscapholide (**4**) will be described.

***γ*-Lactonization from (±)-(4,5-*anti*)-5-Benzyloxy-4-hydroxy-(2*E*)-hexenoic acid (17) (Synthesis of (±)-18) (Chart 3)** The (4*R*,5*S*)-5-hydroxy-2-hexen-4-olide (**3**) having antifeeding activites for the larvae of the yellow butterfly, *Eurema hecabe mandarina* de L'orza, was isolated from *Osmunda japonica* Thunb.[5] The asymmetric synthesis of (4*R*,5*S*)-**3** was reported based on the baker's yeast mediated asymmetric reduction of 1-phenylthio-2,3-butandiones.[6] In order to examine the above mentioned methodology for *γ*-lactone formation, the synthesis of (±)-(4,5)-*trans*-5-benzyloxy-2-hexen-4-olide (**18**) from (±)-(4,5-*anti*)-5-benzyloxy-4-hydroxy-(2*E*)-hexenoic acid (**17**) was selected as shown in Chart 3.

The compound (±)-**17** was synthesized from the reported (±)-**11**[3] as shown in Chart 3. The $AlCl_3$ mediated debenzylation[3] of (±)-**11** in *m*-xylene gave (±)-(4,5-*anti*)-4,5-dihydroxy- (2*E*)-hexenoate (**13**) in 66% yield, which was treated with benzaldehyde in the presence of *p*-toluenesulfonic acid (*p*-TsOH) to afford a mixture of acetals [(±)-**14** and (±)-**15**] in 83% yield. Treatment of this mixture with sodium cyanoborohydride [$Na(CN)BH_3$] gave (±)-(4,5-*anti*)-5-benzyloxy-4-hydroxy-(2*E*)-hexenoate (**16**) (78% yield) and (±)-**11** (13% yield). Alkakine hydrolysis of (±)-**16** followed by acid treatment provided the desired acid (±)-**17**, which was subjected to *γ*-lactone formation reaction without further purification. The *trans*-structure of (±)-**17** was confirmed by ^{1}H-NMR analysis. The crude acid (±)-**17** was treated with 2,4,6-trichlorobenzoyl chloride in pyridine to give the desired *γ*-lactone (±)-**18** in 90% overall yield from (±)-**16**. The $AlCl_3$ mediated debenzylation of (±)-**18** in *m*-xylene afforded the racemic natural product (±)-**3** in 82% yield. The NMR data of the synthetic (±)-**18** and (±)-**3** were identical with those of the reported (+)-**18**[7] and (+)-**3**,[7] respectively.

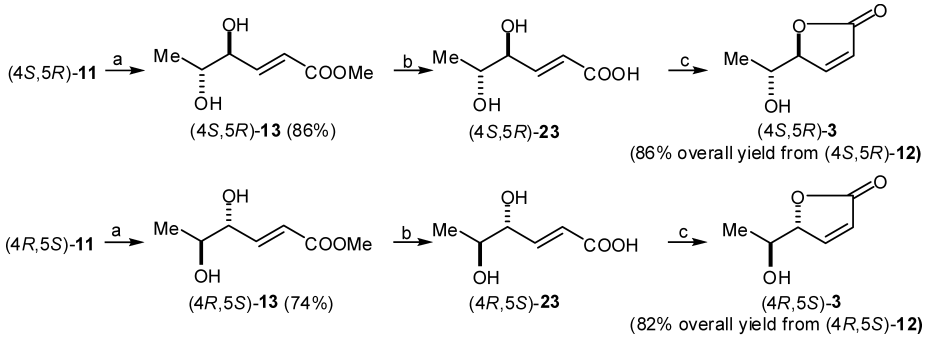
***γ*-Lactonization from (*S*)-4,5-Dihydroxy-(2*E*)-pentenoic Acid (21) (Synthesis of (*S*)-22) (Chart 4)** The (*S*)-5-hydroxy-2-penten-4-olide (**22**) was obtained as an aglycone from a glycoside, ranunculin, which was isolated from *Pulsatilla vulgaris* Mill.[8] It is much interested to reveal whether the formation of the *γ*-lactone formation or *δ*-lactone formation from a (*S*)-4,5-dihydroxy-(2*E*)-pentenoic acid (**21**) may occur. The synthesis of (*S*)-**22** from the commercial available methyl (*S*)-(+)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-*trans*-2-propenoate (**19**) was carried out as shown in Chart 4.

Deprotection of (*S*)-**19** with Dowex 50W (H^+) gave (*S*)-4,5-dihydroxy-(2*E*)-pentenoate (**20**) in 91% yield. Alkakine hydrolysis of (*S*)-**20** followed by acid treatment provided the desired acid (*S*)-**21**, which was subjected to lactone formation reaction without further purification. The *trans*-structure of (*S*)-**21** was confirmed by ^{1}H-NMR analysis. The crude acid (*S*)-**21** was treated with 2,4,6-trichlorobenzoyl chloride in pyridine to give the desired *γ*-lactone (*S*)-**22** in 86% overall yield from



Reagents: a; Dowex 50W (H^+) / H_2O / dioxane b; 1) 2M NaOH / *i*-PrOH 2) 2M HCl
c; 2,4,6-trichlorobenzoyl chloride / pyridine

Chart 4



Reagents: a; $AlCl_3$ / *m*-xylene, CH_2Cl_2 b; 1) 2M NaOH / *i*-PrOH 2) 2M HCl
c; 2,4,6-trichlorobenzoyl chloride / pyridine

Chart 5

(*S*)-**20**. The specific rotation of (*S*)-**22** ($[\alpha]_D^{26}$ −142 (*c*=0.332, H_2O)) was consistent with those of the reported (*S*)-**22** ($[\alpha]_D^{25}$ −145 (*c*=0.126, H_2O).[8] The NMR data of the synthetic (*S*)-**22** were identical with those of the reported (*S*)-**22**.[8] This result is particularly surprising in view of the fact that the γ-lactone formation from (*S*)-**21** occurred in spite of the presence of two hydroxyl groups at C(4)- and C(5)-positions in substrate.

γ-Lactonization from (4*S*,5*R*)- and (4*R*,5*S*)-4,5-Dihydroxy-(2*E*)-hexenoic Acid (23) (Synthesis of (4*S*,5*R*)- and (4*R*,5*S*)-3) (Chart 5) From the result mentioned at Chapter 'γ-Lactonization from (*S*)-4,5-Dihydroxy-(2*E*)-pentenoic Acid (21) (Synthesis of (*S*)-22),' lactone formation of (4*S*,5*R*)- and (4*R*,5*S*)-4,5-dihydroxy-(2*E*)-hexenoic acids (**23**) has aroused our interest as shown in Chart 5.

Deprotection of the reported (4*S*,5*R*)- and (4*R*,5*S*)-**11**[3] by the same way as the preparation of (±)-**13** from (±)-**11** gave (4*S*,5*R*)-**13** (86% yield) and (4*R*,5*S*)-**13** (74% yield), respectively. Alkakine hydrolysis of (4*S*,5*R*)-**13** and (4*R*,5*S*)-**13** followed by acid treatment provided the desired acids (4*S*,5*R*)-**23** and (4*R*,5*S*)-**23**, respectively, which were subjected to lactone formation reaction without further purification. The *trans*-structures of (4*S*,5*R*)-**23** and (4*R*,5*S*)-**23** were separately confirmed by ^{1}H-NMR analysis. The crude acids (4*S*,5*R*)-**23** and (4*R*,5*S*)-**23** were separately treated with 2,4,6-trichlorobenzoyl chloride in pyridine to give the desired γ-lactones (4*S*,5*R*)-5-hydroxy-2-hexen-4-olide (**3**; $[\alpha]_D^{24}$ −176.2 (*c*=0.47, $CHCl_3$), 73% overall yield from (4*S*,5*R*)-**13**) and (4*R*,5*S*)-5-hydroxy-2-hexen-4-olide (**3**; $[\alpha]_D^{23}$ +167.2 (*c*=0.34, $CHCl_3$), 82% overall yield from (4*R*,5*S*)-**13**), respectively. The specific rotation of (4*R*,5*S*)-**3** was consistent with those of the reported (4*R*,5*S*)-**3** ($[\alpha]_D$ +177 (*c*=1.5, $CHCl_3$).[5] The NMR data (^{1}H- and ^{13}C-NMR) of the synthetic (4*S*,5*R*)- and (4*R*,5*S*)-**3** were identical with those of the reported (4*R*,5*S*)-**3**,[5] respectively. The selective formation of (4*S*,5*R*)- and (4*R*,5*S*)-**3** from (4*S*,5*R*)- and (4*R*,5*S*)-**23**, respectively will be discussed at late.

δ-Lactonization from (*S*)-5-Hydroxy-(2*E*)-hexenoic Acid (25) (Synthesis of (*S*)-Parasorbic Acid (1)) (Chart 6) By applying the reported procedure, the starting material (*S*)-5-hydroxy-(2*E*)-hexenoate (**24**) was obtained from the reported (4*R*,5*S*)-**13**.[9] The synthesis of (*S*)-parasorbic acid (**1**) from (*S*)-**24** was shown in Chart 6 (see Chapter 'δ-Lactonization from (5*R*,7*S*)-5,7-Dihydroxy-(2*E*)-octenoic Acid (29) (Synthesis of (5*R*,7*S*)-Euscapholide (4)')). Alkakine hydrolysis of (*S*)-**24** followed by acid treatment provided the desired acid (*S*)-**25** which was subjected to lactone formation reaction without further purification. The *trans*-structures of (*S*)-**25** was confirmed by ^{1}H-NMR analysis. The crude acid (*S*)-**25** was treated with 2,4,6-trichlorobenzoyl chloride in pyridine to give the desired δ-lactone (*S*)-parasorbic acid (**1**; $[\alpha]_D^{21}$ +134.9 (*c*=0.44, EtOH), 70% overall yield from (*S*)-**24**). The NMR data of the synthetic (*S*)-**1** were identical with those of the reported (±)-**1**.[10]

δ-Lactonization from (5*R*,7*S*)-5,7-Dihydroxy-(2*E*)-octenoic Acid (29) (Synthesis of (5*R*,7*S*)-Euscapholide (4)) (Chart 6) The (+)-euscapholide (**4**) was isolated from the leaves of *Euscaphis japonica* and the absolute structure of **4** was deduced to possess 5*R*,7*S*-configurations by means of spectroscopic and chemical analysis.[11] The first total synthesis of (−)-tarchonanthuslactone (**7**) (see Chart 1) having antipodal stereochemistry of (+)-**4** as a partial structure was achieved based on the synthetic strategy of 1,3-*syn*-polyol system[12] but the asymmetric synthesis of (+)-**4** was not achieved. The asymmetric synthesis of (5*R*,7*S*)-**4** from the above mentioned (*S*)-**24** was shown in Chart 6.

For the synthesis of (5*R*,7*S*)-**4**, the synthesis of (5*R*,7*S*)-5,7-dihydroxy-(2*E*)-octenoic acid (**29**) from (*S*)-**24** is necessary. To

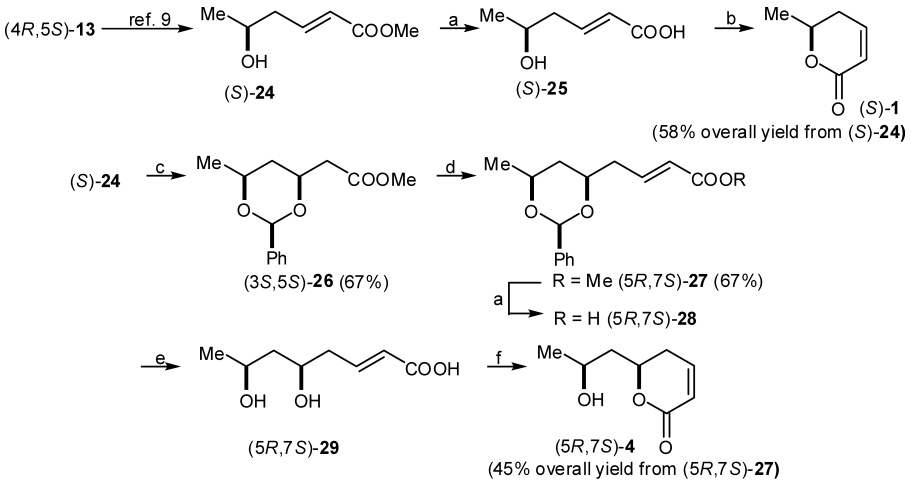


Chart 6

construct the 1,3-*syn*-structure of (5*R*,7*S*)-**29**, (*S*)-**24** was converted into the acetal (3*S*,5*S*)-**26** by applying Evans method.[13] Chiral alcohol (*S*)-**24** was treated with benzaldehyde (PhCHO) in the presence of *tert*-BuOK to give the acetal (3*S*,5*S*)-**26** in 67% yield. The 1,3-*syn*-structure of (3*S*,5*S*)-**26** was confirmed by nuclear Overhauser effect (NOE) measurement as shown in Fig. 1. Diisobutylaluminum hydride (Dibal-H) reduction of (3*S*,5*S*)-**26** followed by treatment of trimethylphosphonoacetate ($(MeO)_2P(O)CH_2COOM$) in the presence of base [LiCl/DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)] afforded the Horner Emmons reaction product (5*R*,7*S*)-**27** in 67% overall yield. Alkakine hydrolysis of (5*R*,7*S*)-**27** followed by acid treatment provided the acid (5*R*,7*S*)-**28** which were subjected to deprotection of benzyl group without further purification to afford the *trans* acid (5*R*,7*S*)-**29**. The *trans*-structure of (5*R*,7*S*)-**29** was confirmed by ^{1}H-NMR analysis. The crude acid (5*R*,7*S*)-**29** was treated with 2,4,6-trichlorobenzoyl chloride in pyridine to give the desired *δ*-lactone (5*R*,7*S*)-**4** ($[\alpha]_D^{22}$ 113.5 (*c*=0.10, MeOH)) in 45% overall yield from (5*R*,7*S*)-**27**. The spectral data (^{1}H- and ^{13}C-NMR) of synthetic (5*R*,7*S*)-**4** were identical with those of the reported (5*R*,7*S*)-**4**.[11] The specific rotation of synthetic (5*R*,7*S*)-**4** was consistent with those of the reported (5*R*,7*S*)-**4** ($[\alpha]_D^{30}$ +115.5 (*c*=1.52, MeOH).[11] Thus the absolute stereochemistry of (+)-euscapholide (**4**) was determined unequivocally to possess 5*R*,7*S*-configurations.

Discussion and Conclusion

As above mentioned in Chapters '*γ*-Lactonization from (*S*)-4,5-Dihydroxy-(2*E*)-pentenoic Acid (21) (Synthesis of (*S*)-22)' and '*γ*-Lactonization from (4*S*,5*R*)- and (4*R*,5*S*)-4,5-Dihydroxy-(2*E*)-hexenoic Acid (23) (Synthesis of (4*S*,5*R*)- and (4*R*,5*S*-3),' the selective *γ*-lactone formation [(*S*)-**22**, (4*S*,5*R*)- and (4*R*,5*S*)-**3**] from 4,5-dihydroxy-2(*E*)-alkenic acid [(*S*)-**21**, (4*S*,5*R*)- and (4*R*,5*S*)-**23**], respectively was occurred. These phenomena could be explained by the fact that the heat of formation of *γ*-lactones [(4*S*,5*R*)- and (4*R*,5*S*)-**3**] is 4.35 kcal/mol stability than that of *δ*-lactones [(4*S*,5*R*)- and (4*R*,5*S*)-**2**] by SPARTAN Hartree–Fock method Molecular Orbital calculation.

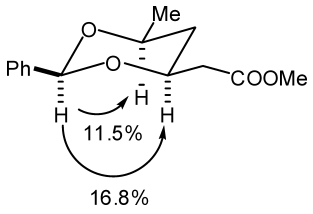


Fig. 1. NOE Correlation of (3*S*,5*S*)-**26**

In conclusion, alkaline hydrolysis of both (±)-(4,5-*anti*)-5-benzyloxy-4-hydroxy-(2*E*)-hexenoate (**16**) and (*S*)-5-hydroxy-(2*E*)-hexenoate (**24**) followed by acid treatment gave the corresponding (2*E*)-hexenoic acids (±)-**17** and (*S*)-**25**, which were subjected to lactone formation reaction without further purification. Both crude acids were treated with 2,4,6-trichlorobenzoyl chloride in pyridine to afford *γ*-lactone [(±)-(4,5)-*trans*-5-benzyloxy-2-hexen-4-olide (**18**; 90% overall yield from (±)-**16**)] and *δ*-lactone [(*S*)-parasorbic acid (**1**; 70% overall yield from (S)-**24**)], respectively, accompanied by *trans–cis* isomerization. Meanwhile (*S*)-4,5-dihydroxy-(2*E*)-pentenoate (**20**) was selectively converted to *γ*-lactone [(*S*)-5-hydroxy-2-penten-4-olide (**22**; 86% overall yield from (*S*)-**20**)] by the above mentioned procedure. The (4*S*,5*R*)- and (4*R*,5*S*)-4,5-dihydroxy-(2*E*)-hexenoates (**13**) were also selectively converted to *δ*-lactone [(4*S*,5*R*)-5-hydroxy-2-hexen-4-olide (**3**; 73% overall yield from (4*S*,5*R*)-**13**) and (4*R*,5*S*)-5-hydroxy-2-hexen-4-olide (**3**; 82% overall yield from (4*R*,5*S*)-**13**), respectively, by the above mentioned procedure. The (*S*)-**24** was converted to (5*R*,7*S*)-5,7-dihydroxy-(2*E*)-octenoic acid (**29**), which was subjected to *δ*-lactone formation reaction by the above mentioned procedure to afford (5*R*,7*S*)-euscapholide (**4**). By the asymmetric synthesis of (5*R*,7*S*)-**4**, the absolute stereochemistry of euscapholide (**4**) was unequivocally determined to possess (5*R*,7*S*)-configurations.

Experimental

^{1}H- and ^{13}C-NMR spectra were recorded on JEOL AL 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. The fast atom

bombardment mass spectra (FAB MS) were obtained with a JEOL JMS 600H spectrometer. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

***γ*-Lactonization from (±)-(4,5-*anti*)-5-Benzyloxy-4-hydroxy-(2*E*)-hexenoic Acid (17) (Synthesis of (±)-18) (Chart 3)** i) To a mixture of $AlCl_3$ (20.8 g, 156 mmol) in CH_2Cl_2 (200 mL) was added a solution of (±)-**11** (13.0 g, 52 mmol) in *m*-xylene (20 mL) at 0°C and the reaction mixture was stirred for 15 min at the same temperature. The reaction mixture was diluted with H_2O and extracted with Et_2O. 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 (300 g, *n*-hexane–AcOEt=1 : 3) to afford (±)-**13** (5.52 g, 66%) as a colorless oil. (±)-**13**: IR (neat): 3410, 1709 cm^{-1}; ^{1}H-NMR δ: 1.12 (3H, d, J=6.0 Hz), 2.85, 3.21 (each 1H, brs), 3.72 (3H, s), 3.92 (1H, brt), 4.72 (1H, m), 6.09 (1H, dd, J=16.0, 2.0 Hz), 6.92 (1H, dd, J=16.0, 5.0 Hz). *Anal.* Calcd for $C_7H_{12}O_4$: C, 56.24; H, 6.29%. Found: C, 56.07; H, 6.37. FAB-MS *m/z*: 161 (M^++1).

ii) A mixture of (±)-**13** (2.133 g, 13.3 mmol), *p*-toluenesulfonic acid 0.25 g, 1.3 mmol) and benzaldehyde (1.62 g, 21.3 mmol) in benzene (30 mL) was refluxed using Dean–Stark apparatus for 4 h. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (80 g, *n*-hexane–AcOEt=50 : 1) to afford a less polar part (±)-**14** (0.982 g, 30%) as a colorless oil and a more polar part. (±)-**15** (1.746 g, 53%) as a colorless oil in elution order: (±)-**14**: IR (neat): 1724 cm^{-1};^{1}H-NMR: δ: 1.23 (3H, d, J=6.0 Hz), 3.76 (3H, s), 4.47 (1H, qd, J=6.0, 6.0 Hz), 4.80 (1H, ddd, J=6.0, 6.0, 1.8 Hz), 6.19 (1H, s, benzylidene H), 6.19 (1H, dd, J=16.0, 1.8 Hz), 6.90 (1H, dd, J=16.0, 6.0 Hz), 7.30–7.47 (5H, m) *Anal.* Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50%. Found: C, 67.26; H, 6.50. FAB-MS *m/z*: 249 (M^++1). (±)-**15**: IR (neat): 1726 cm^{-1}; ^{1}H-NMR δ: 1.26 (3H, d, J=6.0 Hz), 3.73 (3H, s), 4.45 (1H, qd, J=6.0, 6.0 Hz), 4.74 (1H, ddd, J=6.0, 6.0, 1.8 Hz), 5.84 (1H, s, benzylidene H), 6.11 (1H, dd, J=16.0, 1.8 Hz), 6.88 (1H, dd, J=16.0, 6.0 Hz), 7.33–7.53 (5H, m). *Anal.* Calcd for $C_{14}H_{16}O_4 \cdot 0.5H_2O$: C, 65.36; H, 6.66%. Found: C, 65.65; H, 6.30. FAB-MS *m/z*: 249 (M^++1).

iii) $NaBH_3(CN)$ (1.95 g, 30.8 mmol) was added to a 1 : 1.76 mixture (7.647 g, 30.8 mmol) of (±)-**14** and (±)-**15** in MeCN (210 mL) at −20°C and additional $NaBH_3(CN)$ (1.95 g, 30.8 mmol) and $TiCl_4$ (3.39 mL, 30.8 mmol) were added to the above reaction mixture. The reaction mixture was stirred for 40 min at the same temperature. The reaction mixture was diluted with 7% $NaHCO_3$ solution at 0°C and extracted with Et_2O. The organic layer was washed with brine and. dried over $MgSO_4$. Evaporation of organic solvent gave a crude oil, which was chromatographed on silica gel (160 g, *n*-hexane–AcOEt=10 : 1) to give (±)-**16** (6.039 g, 78%) as a colorless oil and (±)-**11** (1.006 g, 13%) in elution order. (±)-**16**: IR (neat): 1726 cm^{-1}; ^{1}H-NMR δ: 1.13 (3H, d, J=6 Hz), 2.38 (1H, d, J=4.4 Hz), 3.66 (1H, qd, J=6.0, 3.0 Hz), 3.73 (3H, s), 4.42 (1H, m), 4.51, 4.62 (each 1H, d, J=12.0 Hz), 6.12 (1H, dd, J=16.0, 2.0 Hz), 6.90 (1H, dd, J=16.0, 5.0 Hz), 7.25–7.38 (5H, m). *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.93; H, 7.35. MS (FAB) *m/z*: 251 (M^++1). NMR data of (±)-**11** were consistent with the authentic (±)-**11**.

iv) To a solution of (±)-**16** (0.985 g, 3.9 mmol) in tetrahydrofuran (THF; 20 mL) was added 2 M NaOH solution (6 mL) and the reaction mixture was stirred for 24 h at rt. The reaction mixture was acidified with 2 M HCl solution and extracted with Et_2O. The organic layer was washed with brine and. dried over $MgSO_4$. Evaporation of organic solvent gave a crude oil (±)-**17** (0.893 g, 96%) as a colorless oil. A part of crude oil (±)-**17** was purified by preparative thin-layer chromatography technique to afford pure (±)-**17**. (±)-**17**: ^{1}H-NMR δ: 1.14 (3H, d, J=6 Hz), 3.68 (1H, qd, J=6.0, 4.0 Hz), 4.47 (1H, m), 4.51, 4.63 (each 1H, d, J=12.0 Hz), 6.13 (1H, dd, J=16.0, 2.0 Hz), 6.99 (1H, dd, J=16.0, 5.0 Hz), 7.25–7.38 (5H, m). *Anal.* Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.80; H, 6.92. MS (FAB) *m/z*: 237 (M^++1).

v) To a solution of (±)-**17** (0.101 g, 0.4 mmol) in pyridine (2 mL) were added 2,4,6-trichlorobenzoyl chloride (0.11 g, 0.47 mmol) and the reaction mixture was stirred for 1 h at rt. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ solution and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane–AcOEt=10 : 1) to afford (±)-**18** (0.085 g, 90% overall yield from (±)-**16**) as a colorless oil. (±)-**18**: ^{1}H-NMR δ: 1.33 (3H, d, J=6 Hz), 3.68 (1H, qd, J=6.0, 4.0 Hz), 4.43, 4.55 (each 1H, d, J=12.0 Hz), 4.91 (1H, m), 6.15 (1H, dd, J=16.0, 2.0 Hz), 7.19–7.32 (5H, m), 7.55 (1H, dd, J=6.0, 2.0 Hz). ^{13}C-NMR δ: 172.8 (s), 153.8 (d), 137.6 (1C, s), 128.4 (2C, d), 128.0 (2C, d), 127.6 (1C, d), 122.3 (d), 85.7 (d), 74.9 (d), 16.6 (q). *Anal.* Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.25; H, 6.67. MS (FAB) *m/z*: 219 (M^++1).

vi) To a suspension of $AlCl_3$ (0.160 g, 1.2 mmol) in CH_2Cl_2 (2 mL) was added a solution of (±)-**18** (0.065 g,0.3 mmol) in *m*-xylene (1.0 mL) at 0°C and the reaction mixture was stirred for 45 min at 0°C. The reaction mixture was poured into ice-H_2O and extracted with Et_2O. The Et_2O 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=1 : 1) to afford (±)-**3** (0.031 g, 82%). (±)-**3**; ^{1}H-NMR δ: 1.28 (3H, d, J=6.0 Hz), 1.70–1.90 (1H, brs), 4.02 (1H, m), 4.91 (1H, m), 6.16 (1H, dd, J=6.0, 2.0 Hz), 7.54 (1H, dd, J=6.0, 2.0 Hz). ^{13}C-NMR δ: 173.0 (s), 153.5 (d), 122.5 (d), 87.0 (d), 67.6 (d), 18.4 (q). *Anal.* Calcd for $C_6H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.51; H, 6.18. MS (FAB) *m/z*: 129 (M^++1).

***γ*-Lactonization from (*S*)-4,5-Dihydroxy-(2*E*)-pentenoic Acid (21) (Synthesis of (*S*)-22) (Chart 4)** i) To a solution of commercially available (*S*)-**19** (0.367 g, 2.0 mmol) in dioxane (10 mL) and H_2O (10 mL) was added Dowex 50W (H+) (2.0 g), and the reaction mixture was stirred for 12 h at 50°C. The reaction mixture was filtered and the filtrate was evaporated to give a crude oil. (*S*)-**20** (0.261 g, 91%) as a colorless oil. (*S*)-**20**: ^{1}H-NMR δ: 2.50 (2H, brs), 3.54 (1H, dd, J=11.0, 7.0 Hz), 3.73 (1H, dd, J=11.0, 3.5 Hz), 3.72 (3H, s), 4.41 (1H, dddd, J=7.0, 4.5, 3.5, 2.0 Hz), 6.13 (1H, dd, J=16.0, 2.0 Hz), 6.89 (1H, dd, J=16.0, 4.5 Hz).

ii) To a solution of crude (*S*)-**20** (0.261 g) in isopropyl alcohol (6.0 mL) was added 2 M NaOH solution (3 mL) and the reaction mixture was stirred for 12 h at rt. The reaction mixture was treated with Et_2O and water layer was acidified

with 2 M HCl solution. The water layer was evaporated to give a crude solid, which was dissolved with MeOH. Evaporation of MeOH afforded (*S*)-**21** (0.237 g, quantitative yield). (*S*)-**21**: IR (KBr): 3342, 1687, 1638 cm^{-1}; ^{1}H-NMR δ: 3.52 (1H, dd, *J*=11.0, 6.0 Hz), 3.56 (1H, dd, *J*=11.0, 5.5 Hz), 4.29 (1H, ddd, *J*=6.0, 5.5, 2.0 Hz), 6.06 (1H, dd, *J*=16.0, 2.0 Hz), 6.97 (1H, dd, *J*=16.0, 5 Hz). *Anal.* Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10. Found: C, 45.29; H, 5.97. MS (FAB) *m/z*: 155 (M^++Na).

iii) To a solution of (*S*)-**21** (0.237 g, 1.8 mmol) in pyridine (5 mL) were added a solution of 2,4,6-trichlorobenzoyl chloride (0.44 g, 1.8 mmol) in CH_2Cl_2 (0.3 mL) at 0°C and the reaction mixture was stirred for 2 h at 0°C. The reaction mixture was treated with 7% aqueous $NaHCO_3$ solution (5 mL) and stirred for 20 min. The reaction mixture was evaporated to give a residue, which was dissolved with Et_2O. The Et_2O soluble part by filtration was dried over $MgSO_4$ and evaporated to afford a residue, which was chromatographed on silica gel (20 g, *n*-hexane–AcOEt=1 : 1) to give (*S*)-**22** (0.177 g, 86% overall yield from (*S*)-**20**). (*S*)-**22**: IR (neat): 3419, 1730, 1579 cm^{-1}; $[\alpha]_D^{26}$ −142 (*c*=0.332, H_2O), ^{1}H-NMR δ: 2.45 (1H, br s), 3.78 (1H, dd, *J*=12.0, 5.0 Hz), 3.98 (1H, dd, *J*=12.0, 4.0 Hz), 5.14 (1H, dddd, *J*=5.0, 4.0, 2.0, 2.0 Hz), 6.19 (1H, dd, *J*=6.0, 2.0 Hz), 7.46 (1H, dd, *J*=6.0, 2.0 Hz). ^{1}H-NMR (CD_3OD) δ: 3.72 (1H, dd, *J*=10.0, 5.0 Hz), 3.88 (1H, dd, *J*=10.0, 4.0 Hz), 5.16 (1H, dddd, *J*=5.0, 4.0, 2.0, 2.0 Hz), 6.19 (1H, dd, *J*=6.0, 2.0 Hz), 7.65 (1H, dd, *J*=6.0, 2.0 Hz). *Anal.* Calcd for $C_5H_6O_3$: C, 52.63; H, 5.30. Found: C, 52.40; H, 5.42. MS (FAB) *m/z*: 115 (M^++1).

γ-Lactonization from (4*S*,5*R*)- and (4*S*,5*R*)-4,5-Dihydroxy-(2*E*)-hexenoic Acid (23) (Synthesis of (4*S*,5*R*)- and (4*R*,5*S*)-3) (Chart 5) i) To a mixture of $AlCl_3$ (2.05 g, 15.2 mmol) in CH_2Cl_2 (15 mL) was added a solution of (4*S*,5*R*)-**11** (0.961 g, 3.8 mmol) in *m*-xylene (2 mL) at 0°C and the reaction mixture was stirred for 15 min at the same temperature. The reaction mixture was worked up in the same way as for (±)-**13** to give (4*S*,5*R*)-**13** (0.530 g, 86%). (4*S*,5*R*)-**13**: $[\alpha]_D^{25}$ −19.9 (*c*=0.58, $CHCl_3$). The spectral data (IR and ^{1}H-NMR) of (4*S*,5*R*)-**13** were identical with those of (±)-**13**. The antipode (4*R*,5*S*)-**13** (0.397 g) was also obtained from (4*R*,5*S*)-**11** (0.835 g, 3.3 mmol) in 74% yield. (4*R*,5*S*)-**13**: $[\alpha]_D^{25}$ +20.1 (*c*=0.47, $CHCl_3$). The spectral data (^{1}H-NMR) of (4*R*,5*S*)-**13** were identical with those of (±)-**13**.

ii) To a solution of (4*S*,5*R*)-**13** (0.480 g, 3.0 mmol) in THF (6.0 mL) was added 2 M NaOH solution (3 mL) and the reaction mixture was stirred for 1 h at rt. The reaction mixture was acidified with 2 M HCl solution and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a crude (4*S*,5*R*)-**23** (0.442 g, quantitative yield), which was used for next reaction without further purification. (4*S*,5*R*)-**23**; $[\alpha]_D^{26}$ −33.9 (*c*=0.49, $CHCl_3$), ^{1}H-NMR (CD_3OD) δ: 1.17 (3H, dd, *J*=6.0 Hz), 3.70 (1H, qt, *J*=6.0, 6.0 Hz), 4.06 (1H, ddd, *J*=6.0, 6.0, 2.0 Hz), 6.04 (1H, dd, *J*=16.0, 2.0 Hz), 7.04 (1H, dd, *J*=16.0, 6.0 Hz). MS (FAB) *m/z*: 145 (M^++1). The antipode (4*R*,5*S*)-**23** (0.075 g) was also obtained from (4*R*,5*S*)-**13** (0.091 g, 0.6 mmol). (4*R*,5*S*)-**23**: $[\alpha]_D^{29}$ +30.3 (*c*=0.31, $CHCl_3$). The spectral data (^{1}H-NMR) of (4*R*,5*S*)-**23** were identical with those of (4*S*,5*R*)-**23**.

iii) To a solution of (4*S*,5*R*)-**23** (0.399 g, 2.7 mmol) in pyridine (10 mL) were added 2,4,6-trichlorobenzoyl chloride (0.72 g, 3.0 mmol) at 0°C and the reaction mixture was stirred for 1 h at rt. The reaction mixture was evaporated to give a residue, which was chromatographed on silica gel (50 g, *n*-hexane–AcOEt=1 : 3) to give (4*S*,5*R*)-**3** (0.280 g, 80% overall yield from (4*S*,5*R*)-**13**). (4*S*,5*R*)-**3**: $[\alpha]_D^{24}$ −176.2 (*c*=0.47, $CHCl_3$), The spectral data (^{1}H- and ^{13}C-NMR) of (4*S*,5*R*)-**3** were identical with those of (±)-**3**. The antipode (4*R*,5*S*)-**3** (0.060 g, 82% overall yield from (4*R*,5*S*)-**13**) was also obtained from (4*R*,5*S*)-**12** (0.091 g). (4*R*,5*S*)-**3**: $[\alpha]_D^{23}$ +167.2 (*c*=0.34, $CHCl_3$). The spectral data (^{1}H-NMR) of (4*R*,5*S*)-**3** were identical with those of (±)-**3**.

δ-Lactonization from (*S*)-5-Hydroxy-(2*E*)-hexenoic Acid (25) (Synthesis of (*S*)-Parasorbic Acid (1)) (Chart 6) i) To a solution of (*S*)-**24** (0.173 g, 1.2 mmol) in THF (2.0 mL) was added 2 M NaOH solution (1.6 mL) and the reaction mixture was stirred for 2.5 h at rt. The reaction mixture was acidified with 2 M H_2SO_4 solution (3.0 mL) and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a crude (*S*)-**25** (0.157 g, quantitative yield), which was used for next reaction without further purification. (*S*)-**25**; ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, dd, *J*=6.0 Hz), 2.35 (2H, dd, *J*=7.0, 7.0 Hz), 3.96 (1H, dq, *J*=7.0, 7.0, 6.0 Hz), 5.85 (1H, d, *J*=16.0 Hz), 6.43–7.71 (1H, br s), 7.02 (1H, dt, *J*=16.0, 7.0 Hz).

ii) To a solution of (*S*)-**25** (0.157 g, 2.7 mmol) in CH_2Cl_2 (2.0 mL) were added 4-dimethylaminopyridine (DMAP, 0.22 g, 1.8 mmol) and 2,4,6-trichlorobenzoyl chloride (0.35 g, 1.4 mmol) at rt and the reaction mixture was stirred for 2 h at rt. Additional DMAP (0.4 g, 1.4 mmol) was added to the above reaction mixture and the reaction mixture was stirred for 2 h at rt. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was washed with 7% $NaHCO_3$ solution and dried over $MgSO_4$.The organic solvent was evaporated to give a residue, which was chromatographed on silica gel (20 g, *n*-hexane–AcOEt=5 : 1) to give (*S*)-**1** (0.078 g, 58% overall yield from (*S*)-**24**). (*S*)-**1**: $[\alpha]_D^{21}$ +134.9 (*c*=0.44, EtOH), IR (neat): 1724, 1390 cm^{-1}; ^{1}H-NMR δ: 1.39 (3H, d, *J*=7.0 Hz), 2.25 (1H, dddd, *J*=18.0, 11.0, 2.0, 2.0 Hz), 2.32 (1H, dddd, *J*=18.0, 6.0, 3.0, 1.0 Hz), 4.52 (1H, ddq, *J*=11.0, 7.0, 3.0 Hz), 5.96 (1H, ddd, *J*=10.0, 2.0, 1.0 Hz), 6.83 (1H, ddd, *J*=10.0, 6.0, 1.0 Hz). *Anal.* Calcd for $C_6H_8O_2$: C, 62.27; H, 7.19. Found: C, 61.99; H, 7.35. MS (FAB) *m/z*: 112 (M^++1).

δ-Lactonization from (5*R*,7*S*)-5,7-Dihydroxy-(2*E*)-octenoic Acid (29) (Synthesis of (5*R*,7*S*)-Euscapholide (4)) (Chart 6) i) To a solution of (*S*)-**24** (0.969 g, 6.7 mmol) in anhydrous THF (50.0 mL) was added benzaldehyde (0.71 g, 6.7 mmol) and *tert*-BuOK (0.075 g, 0.67 mmol) for 15 min at 20°C. This procedure was totally carried out three times and the reaction mixture was stirred for 2 h at the same temperature. To the reaction mixture was added phosphate buffer (pH=7) solution (80 mL) and the reaction mixture was stirred for 10 min. The reaction mixture was condensed to half volume and extracted with Et_2O. 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=25 : 1) to afford (3*S*,5*S*)-**26** (1.124 g, 67%) as a colorless oil. (3*S*,5*S*)-**26**; IR (neat): 1724, 1659 cm^{-1}; $[\alpha]_D^{25}$ +37.5 (*c*=0.46, MeOH); ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, d, *J*=7.0 Hz), 1.42 (1H, ddd, *J*=12.0, 12.0, 13.0 Hz), 1.71 (1H, ddd, *J*=12.0, 3.0, 3.0 Hz), 2.50 (1H, dd, *J*=6.0, 6.0 Hz), 2.73 (1H, dd, *J*=6.0, 6.0 Hz), 3.68 (3H, s), 3.97 (1H, ddq, *J*=13.0, 7.0, 3.0 Hz), 4.30 (1H, dddd, *J*=12.0, 6.0, 6.0, 3.0 Hz), 5.55 (1H, s), 7.28–7.37 (3H, m), 7.46–7.51 (2H, m). *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.98; H, 7.46. MS (FAB) *m/z*: 251 (M^++1).

ii) To a solution of (3*S*,5*S*)-**26** (1.001 g, 4.0 mmol) in

anhydrous toluene (50.0 mL) under argon atmosphere was added a solution of 1 M diisobutylaluminum hydride (Dibal-H) in toluene solution (5.0 mL) at −78°C and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was diluted with H_2O (5 mL) and Et_2O (50 mL) at 0°C and stirred for 30 min. To the above reaction mixture was added 2 M HCl solution (20 mL) and reaction mixture was stirred for 40 min. The reaction mixture was extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a crude aldehyde (0.849 g), which was used for the next reaction without further purification. To a mixture of LiCl (0.17 g, 4 mmol) in CH_3CN (20 mL) at 0°C was added a solution of trimethylphosphonoacetate ($(MeO)_2P(O)CH_2COOMe$; 0.73 g, 4.0 mmol) in CH_3CN (20 mL) at 0°C and the reaction mixture was stirred for 15 min. To the above reaction mixture was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 0.91 g, 6.0 mmol) in CH_3CN (20 mL) and the reaction mixture was stirred for 15 min. To the above reaction mixture was added a solution of the above aldehyde (0.849 g) in CH_3CN (25 mL) at 0°C and the reaction mixture was stirred for 12 h at rt. The reaction mixture was diluted with saturated NH_4Cl solution (40 mL) and a whole mixture was condensed to half volume. It was extracted with Et_2O. 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=10 : 1) to afford (5*R*,7*S*)-**27** (0.744 g, 67%) as a colorless oil. (5*R*,7*S*)-**27**; IR (KBr): 1736 cm^{-1}; $[\alpha]_D^{26}$ +45.7 (*c*=0.52, MeOH); ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, *J*=7.0 Hz), 1.42 (1H, ddd, *J*=13.0, 13.0, 11.0 Hz), 1.61 (1H, ddd, *J*=13.0, 3.0, 3.0 Hz), 2.40–2.47 (1H, m), 2.51–2.61 (1H, m), 3.72 (3H, s), 3.89–3.98 (2H, m), 5.50 (1H, s), 5.91 (1H, dt, *J*=16.0, 12.0 Hz), 7.00 (1H, dd, *J*=16.0, 7.0 Hz), 7.32–7.50 (5H, m). *Anal.* Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.17; H, 7.53. MS (FAB) *m*/*z*: 277 (M^++1).

iii) To a solution of (5*R*,7*S*)-**27** (0.162 g, 0.6 mmol) in iso-PrOH (10.0 mL) was added 2 M NaOH solution (2.0 mL) at 0°C and the reaction mixture was stirred for 12 h at rt. The reaction mixture was condensed to half volume and acidified with 2 M HCl solution (5.0 mL) and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a crude (5*R*,7*S*)-**28** (0.154 g, quantitative yield), which was used for next reaction without further purification. To a solution of (5*R*,7*S*)-**28** (0.154 g) in H_2O (8.0 mL) and dioxane (8.0 mL) was added Dowex 50W (H^+) (1.0 g) and the reaction mixture was stirred for 1.5 h at 130°C. The reaction mixture was filtered and the filtrate was evaporated to afford a crude (5*R*,7*S*)-**29** (0.082 g, 80% yield from (5*R*,7*S*)-**27**), which was used for the next reaction without further purification. (5*R*,7*S*)-**29**; ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, d, *J*=7.0 Hz), 1.52 (1H, ddd, *J*=14.0, 5.0, 5.0 Hz), 1.62 (1H, ddd, *J*=14.0, 8.0, 8.0 Hz), 2.34 (1H, dddd, *J*=14.0, 7.0, 7.0, 2.0 Hz), 2.43 (1H, dddd, *J*=14.0, 7.0, 5.0, 2.0 Hz), 3.88 (1H, dddd, *J*=8.0, 7.0, 5.0, 5.0 Hz), 3.93 (1H, ddq, *J*=8.0, 7.0, 6.0 Hz), 5.86 (1H, dt, *J*=16.0, 2.0 Hz), 6.99 (1H, dt, *J*=16.0, 7.0 Hz).

iv) To a solution of (5*R*,7*S*)-**29** (0.082 g, 0.5 mmol) in pyridine (10 mL) were added a solution of 2,4,6-trichlorobenzoyl chloride (0.16 g, 0.7 mmol) in CH_2C_2 (0.3 mL) and the reaction mixture was stirred for 2.5 h at rt. The reaction mixture was treated with 7% aqueous $NaHCO_3$ solution (3 mL) and stirred for 20 min. The reaction mixture was evaporated to give a residue, which was dissolved with a mixed solvent (Et_2O (5.0 mL) and AcOEt (2 mL)). The organic solvent soluble part by filtration was dried over $MgSO_4$ and evaporated to afford a residue, which was chromatographed on silica gel (20 g, $CHCl_3$–MeOH=25 : 1) to provide (5*R*,7*S*)-**4** (0.041 g, 45% overall yield from (5*R*,7*S*)-**27**) as a homogeneous oil. (5*R*,7*S*)-**4**: $[\alpha]_D^{22}$ 113.5 (*c*=0.10, MeOH), IR ($CHCl_3$): 3420, 1700, 1230, 1200 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, d, *J*=6.0 Hz), 1.74 (1H, ddd, *J*=15.0, 5.0, 4.0 Hz), 1.99 (1H, dt, *J*=15.0, 8.0 Hz), 2.39 (2H, m), 4.07 (1H, m), 4.63 (1H, m), 6.00 (1H, dt, *J*=10.0, 2.0 Hz), 6.88 (1H, ddd, *J*=10.0, 5.5, 3.5 Hz). ^{13}C-NMR (CD_3OD) δ: 166.4 (s), 148.3 (d), 121.3 (d), 77.5 (d), 64.8 (d), 44.7 (t), 30.2 (t), 23.6 (q). *Anal.* Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.77; H, 7.44. MS (FAB) *m*/*z*: 157 (M^++1). The spectral data (^{1}H- and ^{13}C-NMR) of synthetic (5*R*,7*S*)-**4** were identical with those of the reported (5*R*,7*S*)-**4**.

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References

1) Still W. C., Gennari C., *Tetrahedron Lett.*, **24**, 4405–4408 (1983).
2) Chatterjee A. K., Morgan J. P., Scholl M., Grubbs R. H., *J. Am. Chem. Soc.*, **122**, 3783–3784 (2000).
3) Ono M., Saotome C., Akita H., *Tetrahedron Asymmetry*, **7**, 2595–2602 (1996).
4) Ono M., Zhao X. Y., Shida Y., Akita H., *Tetrahedron*, **63**, 10140–10148 (2007).
5) Numata A., Hokimoto K., Takemura T., Katsuno T., Yamamoto K., *Chem. Pharm. Bull.*, **32**, 2815–2820 (1984).
6) Fujisawa T., Kojima E., Sato T., *Chem. Lett.*, **1987**, 2227–2228 (1987).
7) Sanchez-Sancho F., Valverde S., Herradon B., *Tetrahedron Asymmetry*, **7**, 3209–3246 (1996).
8) Boll P. M., Vihavainen T., Selander H., Smidsrød O., *Acta Chem. Scand.*, **22**, 3245–3250 (1968).
9) Nakamura H., Ono M., Shida Y., Akita H., *Tetrahedron Asymmetry*, **13**, 705–713 (2002).
10) Yamagiwa S., Hoshi N., Sato H., Kosugi H., Uda H., *J. Chem. Soc., Perkin Trans. 1*, 214–224 (1978).
11) Takeda Y., Okada Y., Masuda T., Hirata E., Takushi A., Otsuka H., *Phytochemistry*, **49**, 2565–2568 (1998).
12) Nakata T., Hata N., Iida K., Oishi T., *Tetrahedron Lett.*, **28**, 5661–5664 (1987).
13) Evans D. E., Gauchet-Prunet J. A., *J. Org. Chem.*, **58**, 2446–2453 (1993).