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First Diastereoselective Construction of Butane-Type and Butyrolactone-Type Secocyclolignane Structures

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The first diastereoselective construction of butane-type and butyrolactone-type secocyclolignanes was achieved by the application of a high-valency heterobimetallic Ir–Sn complex to benzyl alcohols prepared from an Evans's *anti*-aldol product. The elimination of an acetoxymethyl group to give a cinnamyl structure by using a high-valency heterobimetallic Ir–Sn complex was also observed in this study.

Key words: lignan; secocyclolignane; Ir–Sn complex

The lignans biosynthesized by plants display a variety of chemical structures and biological activities.[1–3] The butanediol **1** and butyrolactone **2** type of lignans (Fig. 1) are well known to be contained in food plants, whose biological activities, adiponectin productive activity,[4] antimicrobial activity,[5] and cytotoxic activity[6] have been reported. Secocyclolignanes **3** and **4**[7] respectively have rearranged structures from **1** and **2**. Thus, the phenyl group at the 7 position of **1** and **2** is moved to the 7′ position, giving the corresponding diphenylmethyl group. Since the structure-biological activity relationship of secocyclolignanes has not been reported, stereoselective synthetic studies are important for biological research. This report describes the diastereoselective construction of the secocylolignane structure.

A key to the synthesis is the availability of the recently reported high-valency heterobimetallic Ir–Sn complex.[8] Benzyl alcohol substrates **5** and **7** could be transformed to secocyclolignane structures **6** and **8**, respectively, by this new Friedel-Crafts reaction (Scheme 1). The Friedel-Crafts reaction using Fe(III) to form the lignan structure has also been reported.[9] In this experiment, benzyloxybenzene was employed as substrate using Ir–Sn complex. The stable protective group of **5** in the presence of a Lewis acid should be selected.

Results and Discussion

For the stereoselective preparation of substrates for the Friedel-Crafts reaction of **16**, **17**, **18**, and **22**, Evans's *anti*-aldol product **9**[10] was employed (Scheme 2). After protection of the secondary hydroxy group of **9** as a triisopropylsilyl ether, $LiBH_4$ reduction, oxidative cleavage of the olefin, pyridinium chlorochromate oxidation, and α-methylation afforded lactone **13**. The $LiAlH_4$ reduction of **13** and subsequent acetylation or benzoylation gave **14** or **15**. Cleavage of silyl ethers **14** and **15** was performed to furnish **16** and **18**, respectively. Diacetate **16** could be converted to *tert*-butyldiphenylsilyl ether **17** by hydrolysis followed by selective silylation. The preparation of substrate **22** began with $LiBH_4$ reduction of **9**, followed by protection of the resulting primary hydroxy group as a pivaloyl ester. Oxidative cleavage of the olefin of **19**, pyridinium chlorochromate oxidation, and α-methylation gave **21**, which was subjected to $LiAlH_4$ reduction followed by benzoylation, giving **22**. Lactone-type substrates **23** and **24** for the synthesis of lactone-type secocyclolignanes were prepared from **12** and **21**, respectively (Scheme 3). Desilylation of **12** gave **23**. On the other hand, treatment of **21** with an aqueous NaOH solution followed by acidification gave desired lactones **24** (31%) and **25** (60%). Primary alcohol **25** could be transformed to **24** in 33% yield by the treatment with an aqueous NaOH solution followed by acidification, recovering **25** in 64% yield.

As the next stage, Friedel-Crafts reactions employing the high-valency heterobimetallic Ir–Sn complex, $[Ir_2(COD)_2(SnCl_3)_2(Cl)_2(\mu\text{-}Cl)_2]$, and the prepared substrates were attempted (Schemes 4 and 5).[8] The reaction of diacetate **16** did not give a Friedel-Crafts product, but unexpected olefin **26** was obtained in 43% yield. It could be assumed that the production of the benzylic cation of **16** was followed by elimination before the Friedel-Crafts reaction. No other olefin derivatives were observed. This acetoxymethyl elimination was also observed in a lower yield when $AlCl_3/Cl(CH_2)_2Cl$ (80 °C, 12 h, 10 mol%, 10% yield; 1 eq., 15% yield), *p*-TsOH/$Cl(CH_2)_2Cl$ (80 °C, 12 h, 30 mol%, 13% yield) and *p*-TsOH/toluene (120 °C, 12 h, 10 mol%, 24% yield) were employed. The elimination product was not obtained when $TiCl_4$, $SnCl_4$ or $[Ir(COD)(\mu\text{-}Cl)]_2$[11] were used. The coupling product was not obtained under these conditions. Olefin **26** was obtained in the highest yield by using $[Ir_2(COD)_2(SnCl_3)_2(Cl)_2(\mu\text{-}Cl)_2]$ which was the best catalyst to get a cinnamyl structure from **16**.

Disilyl ether **17** gave desired secocyclolignane **27** in low 17% yield. Starting material **17** was not recovered, and the production of an olefin such as **26** and olefin derivatives was not observed in this reaction. The desired secocyclolignane structure could be obtained in 75% yield in the reaction with dibenzoate **18**. The production of olefins and olefin derivatives was not observed. Among the protective groups for primary hydroxy groups, a benzoate has been proven to be the most effective to give a secocyclolignane structure.

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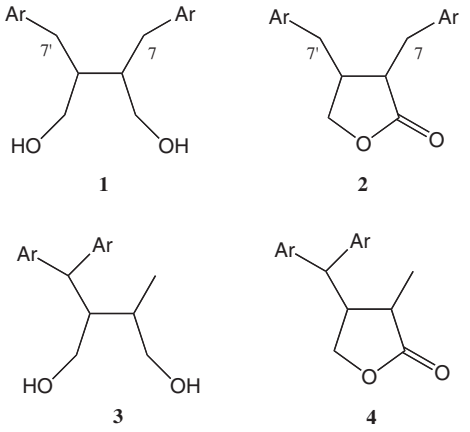
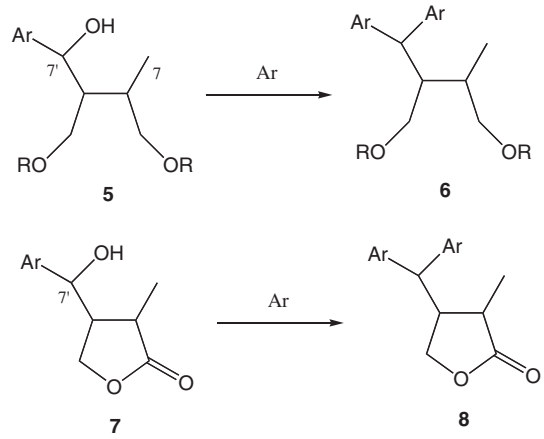
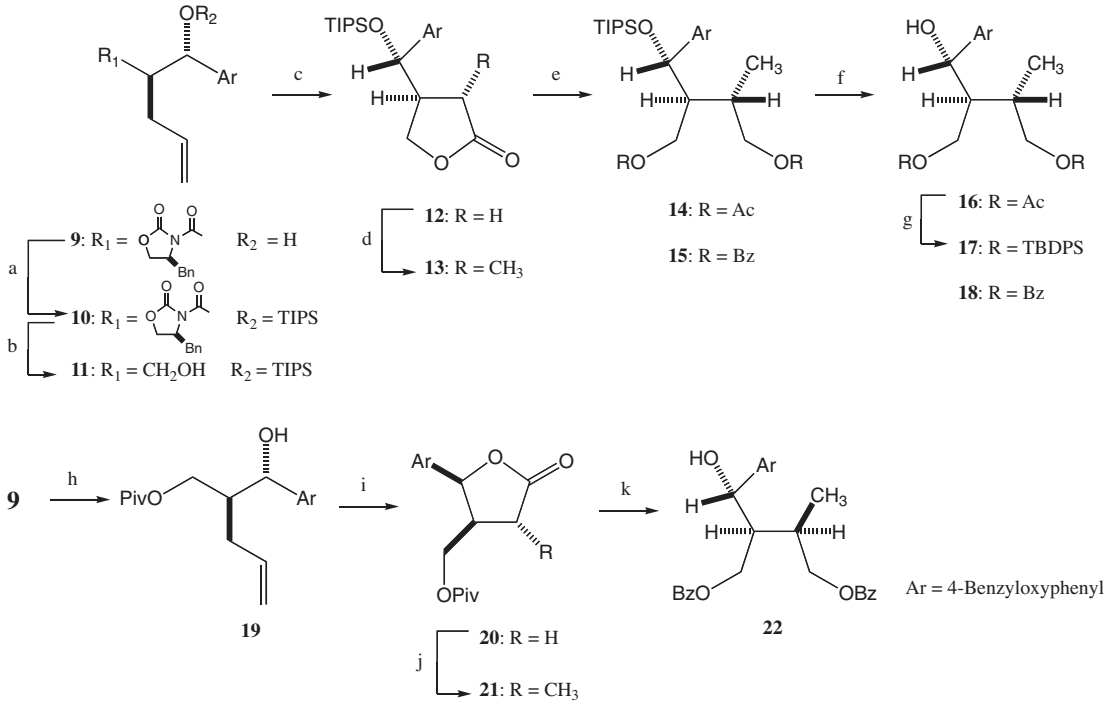


Fig. 1. Butane Lignan **1**, Butyrolactone Lignan **2**, and Secocyclolignanes **3** and **4**.



Scheme 1. Friedel-Crafts Type of Reaction for Benzyl Alcohols **5** and **7**.



Scheme 2. Preparation of Friedel-Crafts Substrates **16**–**18** and **22**.

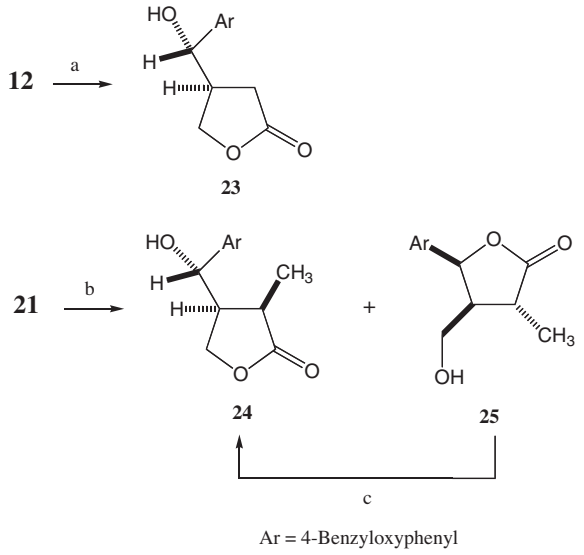
(a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, r.t., 1 h (96% yield); (b) $LiBH_4$, MeOH, THF, r.t., 1 h (59% yield); (c) (1) OsO_4, NMO, aq. acetone, *tert*-BuOH, r.t., 12 h, (2) $NaIO_4$, MeOH, r.t., 1 h, (3) PCC, MS 4A, CH_2Cl_2, r.t., 12 h (76% yield, 3 steps); (d) KHMDS, MeI, THF, −70 °C, 1 h (57% yield, **12** (42%) was recovered); (e) **14**: (1) $LiAlH_4$, THF, 0 °C, 1 h, (2) Ac_2O, Pyr, r.t., 12 h (86% yield, 2 steps), **15**: (1) $LiAlH_4$, THF, 0 °C, 1 h, (2) BzCl, Pyr, r.t., 12 h (64% yield, 2 steps); (f) **16**: (n-Bu)$_4$NF, THF, 0 °C, 1 h (68% yield), **18**: (n-Bu)$_4$NF, THF, 0 °C, 1 h (61% yield); (g) (1) 1 M aq. NaOH solution, EtOH, r.t., 16 h, (2) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, r.t., 1 h (70% yield, 2 steps); (h) (1) $LiBH_4$, MeOH, THF, 0 °C, 1 h, (2) PivCl, Pyr, r.t., 30 min (72% yield, 2 steps); (i) (1) OsO_4, NMO, aq. acetone, *tert*-BuOH, r.t., 12 h, (2) $NaIO_4$, MeOH, r.t., 1 h, (3) PCC, MS 4A, CH_2Cl_2, r.t., 12 h (52% yield, 3 steps); (j) KHMDS, MeI, THF, −70 °C, 1 h (57% yield, **12** (43%) was recovered); (k) (1) $LiAlH_4$, THF, 0 °C, 1 h, (2) BzCl, Pyr, r.t., 12 h (67% yield, 2 steps).

Diastereomeric compound **30** was also obtained from benzoate **22** in 67% yield. No olefin and olefin derivatives were observed. The deprotection of **28** and **30** was performed to give **29** and **31**, respectively. Lactone-type secocyclolignanes **34** and **35** were also respectively obtained from butyrolactones **23** and **24** bearing a benzylic hydroxy group. The Friedel-Crafts reaction of **23** and **24** employing the high-valency heterobimetallic Ir–Sn complex gave a (diphenyl)methyl structure. These products were converted to secocyclolignanes **34** and **35**.

In conclusion, diastereoselective syntheses of secocyclolignane structures were achieved for the first time by using a high-valency heterobimetallic Ir–Sn complex. The cinnamyl structure was obtained by acetoxymethyl elimination when the high-valency heterobimetallic Ir–Sn complex was employed.

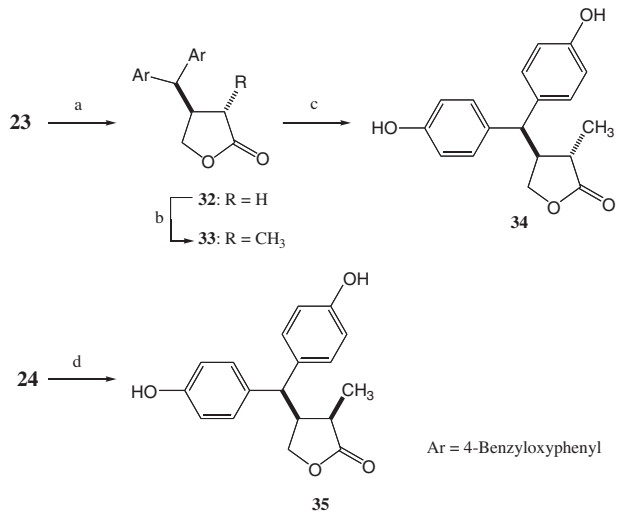
Experimental

General experimental procedures. Melting point (mp) data are uncorrected. NMR data were measured by a JNM-EX400 spectrometer, using TMS as a standard (0 ppm), MS data were measured with a JMS-MS700V spectrometer, and optical rotation values were evaluated with a Horiba SEPA-200 instrument. Elemental analysis was carried out with a Yanako MT-5 CHN coder, and the silica gel used was Wakogel C-300 (Wako, 200–300 mesh).



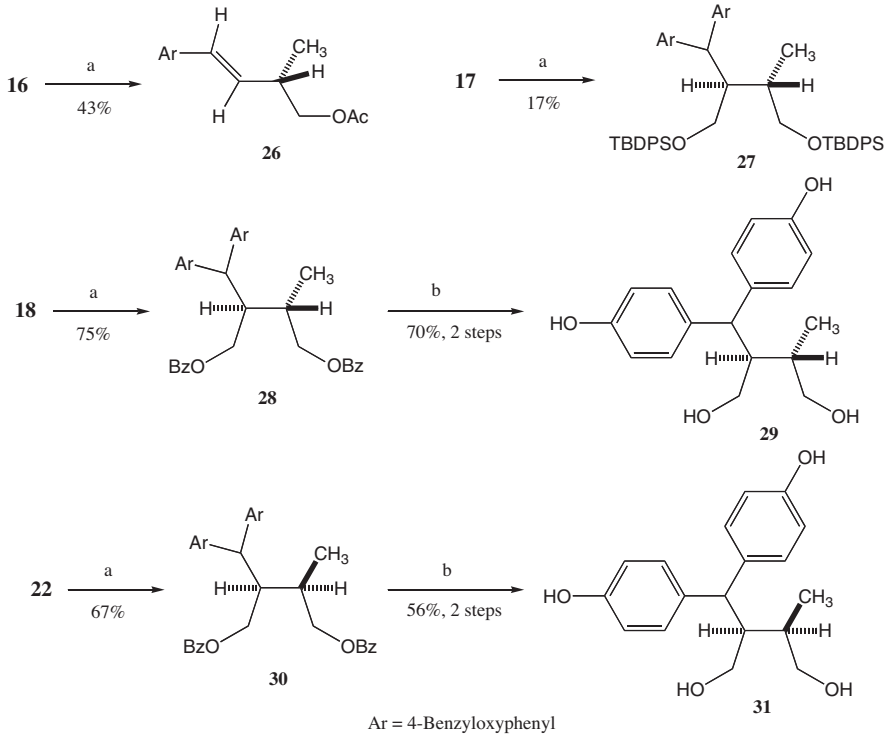
Scheme 3. Preparation of Friedel-Crafts Substrates **23** and **24**.

(a) $(n\text{-Bu})_4NF$, AcOH, THF, r.t., 1 h (60% yield); (b) (1) aq. NaOH, EtOH, r.t., 12 h, (2) 6 M aq. HCl solution (**24**, 31% yield; **25**, 60% yield); (c) (1) aq. NaOH, EtOH, r.t., 12 h, (2) 6 M aq. HCl solution (**24**, 33% yield; **25**, 64% yield).



Scheme 5. Preparation of the Butyrolactone Type of Secocyclolignane Structures.

(a) benzyloxybenzene, $[Ir_2(COD)_2(SnCl_3)_2(Cl)_2(\mu\text{-}Cl)_2]$, $Cl(CH_2)_2Cl$, 80 °C, 12 h (65%); (b) KHMDS, MeI, THF, −70 °C, 1 h (75% yield); (c) H_2, 5% Pd/C, THF, r.t., 6 h (60% yield); (d) (1) benzyloxybenzene, $[Ir_2(COD)_2(SnCl_3)_2(Cl)_2(\mu\text{-}Cl)_2]$, $Cl(CH_2)_2Cl$, 80 °C, 12 h, (2) H_2, 5% Pd/C, THF, r.t., 6 h (56% yield, 2 steps).



Scheme 4. Preparation of the Butane Type of Secocyclolignane Structures.

(a) benzyloxybenzene, $[Ir_2(COD)_2(SnCl_3)_2(Cl)_2(\mu\text{-}Cl)_2]$, $Cl(CH_2)_2Cl$, 80 °C, 12 h; (b) (1) 1 M aq. NaOH, EtOH, r.t., 12 h, (2) H_2, 5% Pd/C, THF, r.t., 6 h.

*(4S)-4-Benzyl-3-{(2R)-2-[(S)-(4-benzyloxyphenyl)(hydroxy)methyl]-4-pentenoyl}-2-oxazolidinone (**9**).* A reaction mixture of (*S*)-4-benzyl-3-(4-pentenyl)-2-oxazolidinone (29.2 g, 0.11 mol), 4-benzyloxybenzaldehyde (22.0 g, 0.10 mol), Et_3N (32.4 ml, 0.23 mol), Me_3SiCl (21.0 ml, 0.17 mol), and $MgCl_2$ (1.10 g, 0.012 mol) in EtOAc (150 ml) was stirred at room temperature for 20 h before filtration through silica gel with ether. The filtrate was concentrated, and then the residue was dissolved in MeOH (250 ml). After addition of CF_3CO_2H (5 ml), the resulting reaction solution was stirred at room temperature for 30 min before addition of Et_3N. The mixture was concentrated, and then the residue was applied to silica gel column chromatography (EtOAc:hexane = 1:3) to give **9** (52.1 g, 0.11 mol, 100%) as a colorless oil, $[\alpha]_D^{20} = -7.4$ (*c* 1.2, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.17 (1H, m), 2.41 (1H, m), 2.60 (1H, dd, J = 13.6, 9.4 Hz), 3.15 (1H, dd, J = 13.6, 3.4 Hz), 3.15 (1H, d, J = 7.5 Hz), 4.06–4.13 (2H, m), 4.53 (1H, m), 4.64 (1H, m), 4.82 (1H, dd, J = 7.5, 7.5 Hz), 4.98 (1H, d, J = 9.3 Hz), 5.03 (1H, d, J = 17.0 Hz), 5.03 (2H, s), 5.72 (1H, m), 6.97 (2H, d, J = 8.7 Hz), 7.12 (2H, d, J = 6.5 Hz), 7.24–7.42 (10H, m). ^{13}C-NMR ($CDCl_3$) δ: 34.2, 37.5, 49.0, 55.3, 65.8, 69.9, 75.5, 114.8, 117.4, 127.2, 127.4, 127.7, 127.9, 128.5, 128.8, 129.4, 134.5, 135.2, 136.8, 153.5, 158.5, 175.4. *Anal.* Found: C, 73.62%; H, 6.35%; N, 2.99%. Calcd. for $C_{29}H_{29}O_5N$: C, 73.87%; H, 6.20%; N, 2.97%.

*(4S)-4-Benzyl-3-{(2R)-2-[(S)-(4-benzyloxyphenyl)(triisopropylsilyloxy)methyl]-4-pentenoyl}-2-oxazolidinone (**10**).* To an ice-cooled solution of **9** (28.2 g, 0.060 mol) and 2,6-lutidine (11.8 ml, 0.10 mol) in CH_2Cl_2 (250 ml) was added TIPSOTf (18.8 ml, 0.07 mol). After the reaction solution was stirred at room temperature for 1 h, sat. aq. $NaHCO_3$ solution was added. The organic solution was separated, washed with sat. aq. $CuSO_4$ solution and sat. aq. $NaHCO_3$ solution, and dried (Na_2SO_4). After evaporation, the residue was recrystallized from *iso*-Pr_2O, giving **10** (36.1 g, 0.058 mol, 96%) as colorless crystals, mp 142–143 °C; $[\alpha]_D^{20} = -29$ (*c* 1.3, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.89–0.98 (21H, m), 1.91 (1H, m), 2.12 (1H, ddd, $J = 13.7$, 9.7, 9.7 Hz), 2.63 (1H, dd, $J = 13.1$, 11.2 Hz), 3.53 (1H, dd, $J = 13.1$, 2.9 Hz), 4.06 (1H, dd, $J = 8.7$, 8.7 Hz), 4.12 (1H, dd, $J = 8.7$, 2.6 Hz), 4.55 (1H, m), 4.61 (1H, m), 4.87 (1H, d, $J = 10.7$ Hz), 4.92 (1H, d, $J = 16.3$ Hz), 5.06 (2H, s), 5.08 (1H, d, $J = 8.4$ Hz), 5.61 (1H, m), 6.94 (2H, d, $J = 8.6$ Hz), 7.24–7.29 (4H, m), 7.32–7.40 (7H, m), 7.44 (1H, d, $J = 7.7$ Hz). ^{13}C-NMR ($CDCl_3$) δ: 12.5, 17.9, 18.0, 34.1, 38.3, 51.4, 55.8, 65.9, 69.9, 114.4, 116.8, 127.2, 127.5, 127.9, 128.5, 128.9, 129.3, 134.7, 134.9, 135.9, 136.9, 153.3, 158.6, 174.6. FABMS *m/z* (%): 628 [$(M + H)^+$, 0.8], 372 (50), 307 (53), 154 (100), 136 (63). HRFABMS *m/z* $(M + H)^+$: calcd. for $C_{38}H_{50}O_5NSi$, 628.3458; found, 628.3461.

*(2S)-2-[(S)-(4-Benzyloxyphenyl)(triisopropylsilyloxy)methyl]-4-penten-1-ol (**11**).* To an ice-cooled solution of $LiBH_4$ (2.15 g, 0.099 mol) in THF (20 ml) were added MeOH (4.30 ml, 0.11 mol) and a solution of **10** (29.0 g, 0.046 mol) in THF (100 ml). The resulting reaction solution was stirred at room temperature for 1 h before addition of sat aq. NH_4Cl solution. After the mixture was concentrated, the residue was dissolved in EtOAc and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Evaporation and subsequent silica gel column chromatography (EtOAc:hexane = 1:7) gave **11** (12.3 g, 0.027 mol, 59%) as a colorless oil, $[\alpha]_D^{20} = -45$ (*c* 1.4, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.86–1.05 (21H, m), 1.85–1.94 (2H, m), 2.19 (1H, m), 2.76 (1H, dd, $J = 5.5$, 5.5 Hz), 3.56 (1H, ddd, $J = 11.1$, 5.8, 5.8 Hz), 3.77 (1H, ddd, $J = 11.1$, 5.5, 2.7 Hz), 4.89 (1H, d, $J = 5.4$ Hz), 4.99 (1H, d, $J = 10.6$ Hz), 5.00 (1H, d, $J = 16.9$ Hz), 5.05 (2H, s), 5.73 (1H, m), 6.93 (2H, d, $J = 8.7$ Hz), 7.25 (2H, d, $J = 8.7$ Hz), 7.32–7.44 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 12.5, 17.9, 18.0, 32.4, 48.3, 63.1, 70.0, 78.1, 114.3, 116.4, 127.5, 127.9, 127.99, 128.02, 128.1, 128.47, 128.51, 135.6, 136.9, 158.1. *Anal*. Found: C, 73.73%; H, 9.05%. Calcd. for $C_{28}H_{42}O_3Si$: C, 73.96%; H, 9.31%.

*(3S)-3-[(S)-(4-Benzyloxyphenyl)(triisopropylsilyloxy)methyl]-4-butanolide (**12**).* A reaction solution of **11** (9.57 g, 0.021 mol) and NMO (3.20 g, 0.027 mol), and OsO_4 (aq. 2% solution, 3 ml) in acetone (240 ml), *tert*-BuOH (60 ml), and H_2O (60 ml) was stirred at room temperature for 12 h before addition of sat. aq. $Na_2S_2O_3$ solution. After concentration of the mixture, the residue was dissolved in EtOAc and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After evaporation, the residue was dissolved in MeOH (200 ml). To this solution was added $NaIO_4$ (5.60 g, 0.026 mol), and then the reaction mixture was stirred at room temperature for 1 h before concentration. The residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, dried (Na_2SO_4), and concentrated. A reaction mixture of the residue, PCC (5.70 g, 0.026 mol), and MS 4A (0.10 g) in CH_2Cl_2 (150 ml) was stirred at room temperature for 12 h before addition of ether and filtration. The filtrate was concentrated, and then the residue was applied to silica gel column chromatography (EtOAc:hexane = 1:4) to give **12** (7.21 g, 0.016 mol, 76%, 3 steps) as a colorless oil, $[\alpha]_D^{20} = -39$ (*c* 1.2, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.93–0.98 (21H, m), 2.31 (2H, d, $J = 8.4$ Hz), 2.85 (1H, m), 4.33 (1H, dd, $J = 9.2$, 7.4 Hz), 4.40 (1H, dd, $J = 9.2$, 6.9 Hz), 4.68 (1H, d, $J = 7.3$ Hz), 5.05 (2H, s), 6.94 (2H, d, $J = 8.7$ Hz), 7.20 (2H, d, $J = 8.7$ Hz), 7.33–7.44 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 12.4, 17.9, 18.0, 31.1, 44.7, 70.0, 70.3, 75.5, 114.8, 127.5, 127.6, 128.0, 128.5, 134.6, 136.7, 158.6, 176.7. *Anal*. Found: C, 71.34%; H, 8.56%. Calcd. for $C_{27}H_{38}O_4Si$: C, 71.32%; H, 8.42%.

*(2S,3S)-3-[(S)-(4-Benzyloxyphenyl)(triisopropylsilyloxy)methyl]-2-methyl-4-butanolide (**13**).* To a solution of KHMDS (21.9 ml, 0.5 M in toluene, 10.9 mmol) in THF (20 ml) was added a solution of **12** (7.00 g, 15.4 mmol) in THF (10 ml) at −70 °C. After the mixture was stirred at −70 °C for 20 min, MeI (1.37 ml, 22.0 mmol) was added. The resulting reaction solution was stirred at −70 °C for 1 h before addition of sat. aq. NH_4Cl solution and EtOAc. The organic solution was separated, washed with brine, dried (Na_2SO_4), and evaporated. The residue was applied to silica gel column chromatography (5% EtOAc in hexane), giving **13** (4.15 g, 8.85 mmol, 57%) as a colorless oil, $[\alpha]_D^{20} = -45$ (*c* 1.2, $CHCl_3$). Lactone **12** (2.93 g, 6.45 mmol, 42%) was recovered. **13**: ^{1}H-NMR ($CDCl_3$) δ: 0.93–0.98 (24H, m), 2.37–2.50 (2H, m), 4.24 (1H, dd, $J = 9.0$, 9.0 Hz), 4.30 (1H, dd, $J = 9.0$, 7.4 Hz), 4.75 (1H, d, $J = 5.4$ Hz), 5.06 (2H, s), 6.95 (2H, d, $J = 8.5$ Hz), 7.19 (2H, d, $J = 8.5$ Hz), 7.33–7.44 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 12.4, 14.4, 17.9, 18.0, 36.5, 52.4, 68.4, 70.0, 75.3, 114.8, 127.5, 127.6, 128.0, 128.5, 134.6, 136.7, 158.6, 179.8. *Anal*. Found: C, 71.71%; H, 8.65%. Calcd. for $C_{28}H_{40}O_4Si$: C, 71.75%; H, 8.60%.

*(2S,3S)-2-[(S)-(4-Benzyloxyphenyl)(triisopropylsilyloxy)methyl]-3-methyltetramethylene diacetate (**14**).* To an ice-cooled suspension of $LiAlH_4$ (0.35 g, 9.22 mmol) in THF (10 ml) was added a solution of **13** (2.00 g, 4.27 mmol) in THF (10 ml). After the reaction mixture was stirred at 0 °C for 1 h, sat. aq. $MgSO_4$ solution and K_2CO_3 were added, and then the resulting mixture was stirred at room temperature for 30 min before filtration. The filtrate was concentrated, and then the residue was dissolved in pyridine (4 ml) and Ac_2O (4 ml). The resulting reaction solution was stood at room temperature for 12 h before addition of ice. After additional 6 h at room temperature, the mixture was dissolved in CH_2Cl_2 and H_2O. The organic solution was separated, washed with 6 M aq. HCl solution and sat. aq. $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated. The residue was applied to silica gel column chromatography (EtOAc:hexane = 1:6), giving **14** (2.04 g, 3.66 mol, 86%, 2 steps) as a colorless oil, $[\alpha]_D^{20} = -14$ (*c* 1.2, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.91–0.97 (24H, m), 1.87 (1H, m), 2.00 (3H, s), 2.02 (1H, m), 2.05 (3H, s), 3.66 (1H, dd, $J = 11.0$, 7.7 Hz), 3.85 (1H, dd, $J = 11.0$, 5.5 Hz), 4.31 (1H, dd, $J = 11.5$, 4.7 Hz), 4.36 (1H, dd, $J = 11.5$, 5.3 Hz), 4.94 (1H, d, $J = 7.6$ Hz), 5.06 (2H, s), 6.93 (2H, d, $J = 8.7$ Hz), 7.25 (2H, d, $J = 8.6$ Hz), 7.30–7.44 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 12.5, 17.1, 17.9, 18.0, 21.1, 31.0, 50.0, 62.1, 66.7, 70.0, 73.6, 114.5, 127.5, 127.9, 128.2, 128.5, 135.5, 136.9, 158.3, 170.8. *Anal*. Found: C, 68.84%; H, 8.73%. Calcd. for $C_{32}H_{48}O_6Si$: C, 69.03%; H, 8.69%.

*(2S,3S)-2-[(S)-(4-Benzyloxyphenyl)(triisopropylsilyloxy)methyl]-3-methyltetramethylene dibenzoate (**15**).* To an ice-cooled suspension of $LiAlH_4$ (0.18 g, 4.74 mmol) in THF (10 ml) was added a solution of **13** (1.00 g, 2.13 mmol) in THF (10 ml). After the reaction mixture was stirred at 0 °C for 1 h, sat. aq. $MgSO_4$ solution and K_2CO_3 were added, and then the resulting mixture was stirred at room temperature for 30 min before filtration. The filtrate was concentrated, and then the residue was dissolved in pyridine (10 ml). To this ice-cooled solution was added BzCl (0.55 ml, 4.74 mmol), and then the reaction mixture was stirred at room temperature for 12 h before additions of H_2O and CH_2Cl_2. The organic solution was separated, washed with 6 M aq. HCl solution and sat. aq. $NaHCO_3$ solution, and dried (Na_2SO_4). Concentration and subsequent silica gel column chromatography (5% EtOAc in hexane) gave **15** (0.93 g, 1.37 mmol, 64%, 2 steps) as a colorless oil, $[\alpha]_D^{20} = +1.5$ (*c* 1.3, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.90–0.96 (21H, m), 1.14 (3H, d, $J = 7.1$ Hz), 2.17 (1H, m), 2.32 (1H, m), 4.01 (1H, dd, $J = 11.0$, 7.5 Hz), 4.18 (1H, dd, $J = 11.0$, 7.2 Hz), 4.63 (1H, dd, $J = 11.6$, 5.3 Hz), 4.68 (1H, dd, $J = 11.6$, 5.9 Hz), 5.03 (2H, s), 5.10 (1H, d, $J = 7.3$ Hz), 6.93 (2H, d, $J = 8.7$ Hz), 7.31–7.43 (12H, m), 7.51–7.55 (2H, m), 7.97–7.99 (2H, m), 8.03 (1H, m). ^{13}C-NMR ($CDCl_3$) δ: 12.5, 17.3, 17.9, 18.1, 31.4, 50.0, 63.1, 67.3, 70.0, 73.8, 114.6, 127.5, 127.9, 128.1, 128.29, 128.33, 128.5, 129.47, 129.52, 130.2, 130.3, 132.8, 132.9, 135.4, 136.9, 158.4, 166.4, 166.5. *Anal*. Found: C, 74.16%; H, 7.89%. Calcd. for $C_{42}H_{52}O_6Si$: C, 74.08%; H, 7.70%.

*(2S,3S)-2-[(S)-(4-Benzyloxyphenyl)(hydroxy)methyl]-3-methyltetramethylene diacetate (**16**).* To an ice-cooled solution of **14** (2.04 g, 3.66 mmol) in THF (10 ml) was added (n-Bu)$_4$NF (4.33 ml, 1 M in THF, 4.33 mol). The reaction solution was stirred at 0 °C for 1 h before additions of sat. aq. NH_4Cl solution and EtOAc. The organic solution was separated, washed with sat. aq. $CuSO_4$ solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Concentration and subsequent

silica gel column chromatography (EtOAc:hexane = 1:2) gave **16** (1.00 g, 2.50 mmol, 68%) as a colorless oil, $[\alpha]_D^{20} = -7.2$ (*c* 1.3, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, d, $J = 6.8$ Hz), 1.96–2.03 (2H, m), 1.98 (3H, s), 2.03 (3H, s), 2.51 (1H, br. s), 3.88 (1H, dd, $J = 11.1$, 6.9 Hz), 4.06 (1H, dd, $J = 11.1$, 5.7 Hz), 4.29 (1H, dd, $J = 11.4$, 4.3 Hz), 4.33 (1H, dd, $J = 11.4$, 5.2 Hz), 4.81 (1H, d, $J = 5.2$ Hz), 5.05 (2H, s), 6.96 (2H, d, $J = 8.6$ Hz), 7.25 (2H, d, $J = 8.6$ Hz), 7.30–7.43 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 15.9, 20.85, 20.93, 32.2, 47.4, 61.9, 66.9, 70.0, 72.5, 114.8, 127.2, 127.3, 127.35, 127.39, 127.9, 128.5, 135.5, 136.8, 158.2, 170.9, 171.0. *Anal*. Found: C, 68.97%; H, 7.20%. Calcd. for $C_{23}H_{28}O_6$: C, 68.98%; H, 7.05%.

*(1S,2S,3S)-1-(4-Benzyloxyphenyl)-4-(*tert*-butyldiphenylsilyloxy)-2-(*tert*-butyldiphenylsilyloxymethyl)-3-methyl-1-butanol (**17**).* A reaction solution of **16** (0.22 g, 0.55 mmol) in EtOH (10 ml) and 1 M aq. NaOH solution was stirred at room temperature for 16 h. After additions of H_2O and $CHCl_3$, the organic solution was separated, dried (Na_2SO_4), and concentrated. A reaction solution of the residue, TBDPSCl (0.29 ml, 1.10 mmol), Et_3N (0.17 ml, 1.22 mmol), and DMAP (3 mg, 0.025 mmol) in CH_2Cl_2 (5 ml) was stirred at room temperature for 1 h before additions of H_2O and CH_2Cl_2. The organic solution was separated, dried (Na_2SO_4), and evaporated. The residue was applied to silica gel column chromatography (EtOAc:hexane = 1:6) to give **17** (0.30 g, 0.38 mmol, 70%) as a colorless oil, $[\alpha]_D^{20} = +11$ (*c* 0.8, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, d, $J = 6.8$ Hz), 1.06 (18H, s), 1.92 (1H, m), 1.96 (1H, m), 3.36 (1H, dd, $J = 10.2$, 4.8 Hz), 3.44 (1H, dd, $J = 10.2$, 4.5 Hz), 3.75 (1H, dd, $J = 10.7$, 5.0 Hz), 3.79 (1H, dd, $J = 10.7$, 3.4 Hz), 4.53 (1H, d, $J = 5.1$ Hz), 4.97 (1H, dd, $J = 5.1$, 5.1 Hz), 5.05 (2H, s), 6.90 (2H, d, $J = 8.7$ Hz), 7.22–7.46 (19H, m), 7.50–7.57 (4H, m), 7.69–7.72 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 19.0, 26.5, 34.1, 48.4, 63.5, 65.9, 70.0, 75.7, 114.5, 127.3, 127.5, 127.56, 127.58, 127.7, 127.8, 127.9, 128.6, 129.55, 129.61, 129.8, 129.9, 132.4, 132.5, 133.5, 133.6, 134.8, 135.2, 135.5, 135.59, 135.64, 136.6, 137.2, 157.8. FABMS m/z (%): 793 [$(M + H)^+$, 2], 135 (79), 91 (100). HRFABMS m/z $(M + H)^+$: calcd. for $C_{51}H_{61}O_4Si_2$, 793.41090; found, 793.41090.

*(2S,3S)-2-[(S)-(4-Benzyloxyphenyl)(hydroxy)methyl]-3-methyltetramethylene dibenzoate (**18**).* Title compound **18** was obtained from **15** by the same method as that described for the synthesis of compound **16** in 61% yield as a colorless oil, $[\alpha]_D^{20} = +8$ (*c* 1.7, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, d, $J = 6.8$ Hz), 2.20–2.30 (2H, m), 2.55 (1H, d, $J = 3.8$ Hz), 4.24 (1H, dd, $J = 11.1$, 6.8 Hz), 4.38 (1H, dd, $J = 11.1$, 5.6 Hz), 4.59 (1H, dd, $J = 11.7$, 3.6 Hz), 4.68 (1H, dd, $J = 11.7$, 5.4 Hz), 4.96 (1H, dd, $J = 3.8$, 3.8 Hz), 4.99 (2H, s), 6.93 (2H, d, $J = 8.7$ Hz), 7.28–7.40 (11H, m), 7.42–7.55 (2H, m), 7.93–8.00 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 16.0, 32.7, 47.8, 62.5, 67.5, 70.0, 72.6, 114.9, 127.3, 127.4, 127.9, 128.3, 128.5, 129.4, 129.5, 129.9, 130.1, 132.9, 133.0, 135.5, 136.9, 158.3, 166.4, 166.6. *Anal*. Found: C, 75.31%; H, 6.34%. Calcd. for $C_{33}H_{32}O_6$: C, 75.55%; H, 6.15%.

*(2S)-2-[(S)-(4-Benzyloxyphenyl)(hydroxy)methyl]-4-pentenyl pivaloate (**19**).* To a solution of **9** (23.3 g, 49.4 mmol) and MeOH (4.3 ml) in THF (260 ml) was added a solution of $LiBH_4$ (2.15 g, 98.7 mmol) in THF (115 ml) at below 0 °C, and then the resulting reaction solution was stirred at 0 °C for 1 h. After additions of 1 M aq. NaOH solution and EtOAc, the organic solution was separated, washed with brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in pyridine (20 ml). To the ice-cooled solution was added PivCl (6.10 ml, 49.5 mmol), and then the resulting reaction mixture was stirred at room temperature for 30 min before additions of CH_2Cl_2 and H_2O. The organic solution was separated, washed with 6 M aq. HCl solution and sat. aq. $NaHCO_3$, and dried (Na_2SO_4). Concentration and subsequent silica gel column chromatography (EtOAc:hexane = 1:5) gave **19** (13.6 g, 35.6 mmol, 72%) as a colorless oil, $[\alpha]_D^{20} = -0.8$ (*c* 1.2, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.22 (9H, s), 1.92 (1H, m), 2.02–2.08 (2H, m), 2.56 (1H, br. s), 4.09 (1H, dd, $J = 11.2$, 4.3 Hz), 4.36 (1H, dd, $J = 11.2$, 4.3 Hz), 4.54 (1H, d, $J = 7.1$ Hz), 4.98 (1H, d, $J = 13.7$ Hz), 5.03 (1H, d, $J = 12.3$ Hz), 5.05 (2H, s), 5.70 (1H, m), 6.95 (2H, d, $J = 8.7$ Hz), 7.23 (2H, d, $J = 8.7$ Hz), 7.30–7.44 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 27.2, 32.2, 38.9, 44.9, 63.1, 70.0, 70.1, 114.8, 117.0, 127.4, 127.7, 127.9, 128.5, 134.9, 135.7, 136.9, 158.3, 178.7. *Anal*. Found: C, 75.30%; H, 7.99%. Calcd. for $C_{24}H_{30}O_4$: C 75.36%; H, 7.91%.

*(3S,4S)-4-(4-Benzyloxyphenyl)-3-pivaloyloxymethyl-4-butanolide (**20**).* Compound **19** was converted to compound **20** as colorless crystals, mp 83–84 °C (*iso*-Pr_2O), in 52% yield by the same method as that described for the synthesis of compound **12**, $[\alpha]_D^{20} = -0.8$ (*c* 1.2, $CHCl_3$). ^{1}H-NMR (acetone-d_6) δ: 1.13 (9H, s), 2.56 (1H, dd, $J = 17.2$, 4.0 Hz), 2.94 (1H, dd, $J = 17.2$, 8.8 Hz), 3.20 (1H, m), 3.63 (1H, dd, $J = 11.4$, 5.1 Hz), 3.81 (1H, dd, $J = 11.4$, 5.2 Hz), 5.12 (2H, s), 5.77 (1H, d, $J = 6.8$ Hz), 7.06 (2H, d, $J = 8.7$ Hz), 7.31 (2H, d, $J = 8.7$ Hz), 7.34–7.43 (3H, m), 7.47–7.69 (2H, m). ^{13}C-NMR (acetone-d_6) δ: 27.1, 32.7, 38.9, 39.8, 63.7, 70.3, 82.5, 115.4, 116.4, 127.6, 128.2, 128.4, 129.02, 129.04, 137.94, 159.4, 176.0, 177.7. *Anal.* Found: C, 71.97%; H, 6.86%. Calcd. for $C_{23}H_{26}O_5$: C, 72.23%; H, 6.85%.

*(2R,3S,4S)-4-(4-Benzyloxyphenyl)-2-methyl-3-pivaloyloxymethyl-4-butanolide (**21**).* Compound **20** was converted to compound **21** as a colorless oil in 57% yield by the same method as that described for the synthesis of compound **13**. Compound **20** was recovered in 43%. **21**: $[\alpha]_D^{20} = +36$ (*c* 1.5, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.17 (9H, s), 1.37 (3H, d, $J = 7.0$ Hz), 2.61 (1H, m), 2.74 (1H, m), 3.70 (1H, dd, $J = 11.4$, 7.1 Hz), 3.80 (1H, dd, $J = 11.4$, 5.7 Hz), 5.04 (2H, s), 5.62 (1H, d, $J = 7.8$ Hz), 6.95 (2H, d, $J = 8.6$ Hz), 7.13 (2H, d, $J = 8.6$ Hz), 7.31–7.43 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 14.7, 27.1, 36.6, 38.6, 46.6, 62.9, 70.0, 80.2, 114.8, 114.9, 126.4, 127.0, 127.40, 127.43, 128.0, 128.5, 136.5, 158.9, 177.9, 178.7. FABMS m/z (%): 397 [$(M + H)^+$, 19], 91 (100). HRFABMS m/z $(M + H)^+$: calcd. for $C_{24}H_{29}O_5$, 397.2015; found, 397.2017.

*(2S,3R)-2-[(S)-(4-Benzyloxyphenyl)(hydroxy)methyl]-3-methyltetramethylene dibenzoate (**22**).* Compound **21** was converted to compound **22** as a colorless oil in 67% yield by the same method as that described for the synthesis of compound **15**, $[\alpha]_D^{20} = -32$ (*c* 0.8, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, d, $J = 7.0$ Hz), 2.11 (1H, m), 2.42 (1H, m), 2.57 (1H, br. s), 4.31 (1H, dd, $J = 11.1$, 6.3 Hz), 4.37 (1H, dd, $J = 11.1$, 7.2 Hz), 4.62–4.69 (2H, m), 4.85 (1H, d, $J = 7.4$ Hz), 5.01 (2H, s), 6.93 (2H, d, $J = 8.7$ Hz), 7.29 (2H, d, $J = 8.7$ Hz), 7.31–7.40 (9H, m), 7.42–7.57 (2H, m), 7.96–8.00 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 13.4, 32.2, 45.9, 62.6, 68.2, 70.0, 73.2, 114.9, 127.4, 128.0, 128.4, 128.54, 129.45, 129.49, 129.6, 130.0, 130.2, 132.9, 135.1, 136.9, 158.4, 166.4, 166.7; FABMS m/z (%): 525 [$(M + H)^+$, 0.7], 154 (78), 91 (100). HRFABMS m/z $(M + H)^+$: calcd. for $C_{33}H_{33}O_6$, 525.2277; found, 525.2275.

*(S)-3-[(S)-(4-Benzyloxyphenyl)(hydroxy)methyl]-4-butanolide (**23**).* To an ice-cooled solution of **12** (1.84 g, 4.05 mmol) in THF (10 ml) were added AcOH (0.25 ml, 4.37 mmol) and $(n\text{-Bu})_4NF$ (6.05 ml, 1 M in THF, 6.05 mmol). After the resulting reaction solution was stirred at room temperature for 1 h before additions of sat. aq. $NaHCO_3$ solution and EtOAc. The organic solution was separated, washed with sat. aq. $CuSO_4$ solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Concentration and subsequent silica gel column chromatography (EtOAc:hexane = 1:2) gave **23** (0.72 g, 2.41 mmol, 60%) as colorless crystals, mp 95–96 °C (EtOAc), $[\alpha]_D^{20} = -38$ (*c* 0.8, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.22 (1H, dd, $J = 17.9$, 7.3 Hz), 2.35 (1H, dd, $J = 17.9$, 9.0 Hz), 2.42 (1H, s), 2.84 (1H, m), 4.36 (1H, dd, $J = 9.5$, 6.2 Hz), 4.40 (1H, dd, $J = 9.5$, 6.5 Hz), 4.53 (1H, d, $J = 7.9$ Hz), 5.05 (2H, s), 6.95–6.97 (2H, m), 7.21–7.25 (2H, m), 7.31–7.43 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 31.3, 42.4, 70.0, 70.5, 74.9, 115.1, 127.3, 127.4, 128.0, 128.6, 134.1, 136.7, 158.8, 176.9. *Anal*. Found: C, 72.08%; H, 5.98%. Calcd. for $C_{18}H_{18}O_4$: C, 72.47%; H, 6.08%.

*(2R,3S)-3-[(S)-(4-Benzyloxyphenyl)(hydroxy)methyl]-2-methyl-4-butanolide (**24**) and (2R,3S,4S)-4-(4-benyzloxyphenyl)-3-hydroxymethyl-2-methyl-4-butanolide (**25**).* A reaction solution of **21** (1.81 g, 4.57 mmol) in EtOH (20 ml) and 1 M aq. NaOH solution (20 ml) was stirred at room temperature for 12 h before additions of 6 M aq. HCl solution and $CHCl_3$. The organic solution was separated, washed with sat. aq. $NaHCO_3$ solution, and dried (Na_2SO_4). Concentration and subsequent silica gel column chromatography (EtOAc:hexane = 1:1) gave **24** (0.44 g, 1.41 mmol, 31%) and **25** (0.86 g, 2.75 mmol, 60%). **24**: Mp 138–139 °C (*iso*-Pr_2O), $[\alpha]_D^{20} = -58$ (*c* 0.2, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, d, $J = 7.3$ Hz), 1.81 (1H, d, $J = 3.4$ Hz), 2.68 (1H, m), 2.80 (1H, m), 4.22 (1H, dd, $J = 9.6$, 6.9 Hz), 4.37 (1H, dd, $J = 9.6$, 4.1 Hz), 4.90 (1H, dd, $J = 4.5$, 3.4 Hz), 5.08 (2H, s), 6.98–

7.01 (2H, m), 7.24–7.30 (2H, m), 7.32–7.45 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 10.3, 36.6, 45.1, 67.4, 70.1, 71.5, 115.2, 127.1, 127.5, 128.1, 128.6, 134.2, 136.7, 141.6, 158.7, 179.7. EIMS m/z (%) 312 (M^+, 65), 213 (100), 91 (99). HREIMS m/z M^+: calcd. for $C_{19}H_{20}O_4$, 312.1362; found, 312.1362. **25**: Mp 81–82 °C (*iso*-Pr_2O), $[\alpha]_D^{20}$ = +9.5 (*c* 0.4, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, d, J = 6.7 Hz), 1.58 (1H, br. s), 2.61–2.67 (2H, m), 3.32 (1H, br. m), 3.51 (1H, br. d, J = 11.0 Hz), 5.06 (2H, s), 5.63 (1H, d, J = 7.0 Hz), 6.98–7.00 (2H, m), 7.19 (2H, d, J = 8.7 Hz), 7.31–7.43 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 14.6, 35.7, 49.7, 61.0, 70.1, 80.6, 115.1, 127.1, 127.5, 128.1, 128.7, 158.9, 179.4. EIMS m/z (%): 312 (M^+, 99), 213 (38), 91 (100). HREIMS m/z M^+: calcd. for $C_{19}H_{20}O_4$, 312.1362; found, 312.1362. A reaction solution of **25** (0.86 g, 2.75 mmol) in EtOH (15 ml) and 1 M aq. NaOH solution (15 ml) was stirred at room temperature for 12 h before additions of 6 M aq. HCl solution and $CHCl_3$. The organic solution was separated, washed with sat. aq. $NaHCO_3$ solution, and dried (Na_2SO_4). Concentration and subsequent silica gel column chromatography (EtOAc:hexane = 1:1) gave **24** (0.28 g, 0.90 mmol, 33%) and **25** (0.55 g, 1.76 mmol, 64%).

*(*E*)-(*S*)-4-(4-Benzyloxyphenyl)-2-methyl-3-buten-1-yl acetate (**26**).* A reaction mixture of **16** (112 mg, 0.28 mmol), benzyloxybenzene (63 mg, 0.34 mmol), and $[Ir_2(COD)_2(SnCl_3)_2(Cl)_2(\mu\text{-}Cl)_2]$ (3 mg, 0.0025 mmol) in $Cl(CH_2)_2Cl$ (1 ml) was stirred at 80 °C for 12 h before addition of a few drops of Et_3N and concentration. The residue was applied to silica gel column chromatography (5% EtOAc in hexane) to give **26** (36 mg, 0.12 mmol, 43%) as a colorless oil, $[\alpha]_D^{20} = -39$ (*c* 0.1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, d, J = 6.8 Hz), 2.05 (3H, s), 2.66 (1H, m), 3.98 (1H, dd, J = 10.7, 6.6 Hz), 4.06 (1H, dd, J = 10.7, 7.0 Hz), 5.07 (2H, s), 5.96 (1H, dd, J = 16.3, 7.4 Hz), 6.37 (1H, d, J = 16.3 Hz), 6.92 (2H, d, J = 8.7 Hz), 7.28 (2H, d, J = 8.7 Hz), 7.32–7.44 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 17.0, 21.0, 36.5, 68.6, 70.0, 114.9, 127.3, 127.4, 128.0, 128.6, 129.6, 129.7, 130.4, 137.0, 158.1, 171.2. EIMS m/z (%): 310 (M^+, 12), 250 (94), 91 (100). HREIMS m/z M^+: Calcd. for $C_{20}H_{22}O_3$, 310.1569; found, 310.1570.

*(2*S*,3*S*)-1,1-Bis(4-benzyloxyphenyl)-4-(*tert*-butyldiphenylsilyloxy)-2-(*tert*-butyldiphenylsilyloxy)methyl-3-methylbutane (**27**).* Compound **27** was obtained from **17** by the same method as that described for the synthesis of **26** in 17% yield as a colorless oil, $[\alpha]_D^{20} = +8$ (*c* 0.5, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (9H, s), 0.99 (9H, s), 1.02 (3H, d, J = 7.0 Hz), 2.09 (1H, m), 2.44 (1H, m), 3.44 (1H, dd, J = 9.9, 9.9 Hz), 3.57 (2H, d, J = 4.1 Hz), 3.74 (1H, dd, J = 9.9, 5.4 Hz), 3.94 (1H, d, J = 11.9 Hz), 4.96 (2H, s), 4.97 (2H, s), 6.73 (2H, d, J = 8.7 Hz), 6.80 (2H, d, J = 8.7 Hz), 7.03 (2H, d, J = 8.7 Hz), 7.08 (2H, d, J = 8.7 Hz), 7.17–7.21 (2H, m), 7.26–7.48 (24H, m), 7.56–7.60 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 19.0, 19.2, 26.9, 36.3, 46.9, 50.0, 62.5, 66.8, 69.9, 70.0, 114.7, 114.8, 127.35, 127.42, 127.46, 127.51, 127.88, 128.55, 128.65, 128.82, 129.3, 129.4, 133.3, 133.4, 134.1, 134.2, 135.5, 135.59, 135.64, 135.7, 137.0, 137.3, 156.97, 157.04. FABMS m/z (%): 959 [$(M + H)^+$, 0.6], 91 (100). HRFABMS m/z $(M + H)^+$: calcd. for $C_{64}H_{71}O_4Si_2$, 959.4891; found, 959.4893.

*(2*S*,3*S*)-2-[Bis(4-benzyloxyphenyl)]methyl-3-methyltetramethylene dibenzoate (**28**).* Compound **28** was obtained from **18** by the same method as that described for the synthesis of **26** in 75% yield as a colorless oil, $[\alpha]_D^{20} = -32$ (*c* 1.9, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, d, J = 7.0 Hz), 2.34 (1H, m), 2.80 (1H, m), 4.15 (1H, d, J = 12.0 Hz), 4.20 (1H, dd, J = 11.5, 6.5 Hz), 4.24 (1H, dd, J = 11.5, 5.8 Hz), 4.40 (1H, dd, J = 10.8, 5.9 Hz), 4.42 (1H, dd, J = 10.8, 3.1 Hz), 4.91 (2H, s), 4.98 (2H, s), 6.81 (2H, d, J = 8.7 Hz), 6.90 (2H, d, J = 8.7 Hz), 7.18–7.21 (2H, m), 7.27–7.42 (16H, m), 7.51–7.55 (2H, m), 7.96–8.00 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 16.8, 32.7, 44.9, 50.9, 63.8, 66.9, 69.9, 70.0, 115.0, 115.1, 127.4, 127.5, 127.8, 127.9, 128.30, 128.34, 128.47, 128.49, 128.53, 128.7, 129.5, 130.0, 130.3, 132.8, 132.9, 135.8, 136.97, 136.99, 157.36, 157.39, 166.21, 166.43. EIMS m/z (%): 690 (M^+, 23), 477 (99), 469 (82), 380 (100), 289 (83), 263 (99). HREIMS m/z M^+: calcd. for $C_{46}H_{42}O_6$, 690.2982; found, 690.2982.

*(2*S*,3*S*)-2-[Bis(4-hydroxyphenyl)]methyl-3-methyl-1,4-butanediol (**29**).* A reaction solution of **28** (0.30 g, 0.43 mmol) in EtOH (20 ml) and 1 M aq. NaOH solution (20 ml) was stirred at room temperature for 12 h before additions of H_2O and $CHCl_3$. The organic solution was separated, dried (Na_2SO_4), and concentrated. A reaction mixture of the residue and 5% Pd/C (0.30 g) in THF (25 ml) was stirred under H_2 gas at the ambient temperature for 6 h before filtration. The filtrate was concentrated, and then the residue was recrystallized from MeOH to give **29** (0.093 g, 0.31 mmol, 72%) as colorless crystals, mp 207–208 °C, $[\alpha]_D^{20} = -15$ (*c* 0.1, MeOH). ^{1}H-NMR (C_5D_5N) δ: 1.34 (3H, d, J = 7.1 Hz), 2.39 (1H, m), 2.67 (1H, m), 3.80 (1H, dd, J = 11.2, 4.3 Hz), 3.88 (1H, dd, J = 11.2, 4.4 Hz), 4.10 (1H, dd, J = 8.2, 0.9 Hz), 4.20 (1H, dd, J = 8.2, 3.9 Hz), 4.63 (1H, d, J = 12.0 Hz), 5.60–6.60 (2H, br.), 7.14–7.21 (4H, m), 7.51–7.58 (4H, m), 11.0–11.6 (2H, br.). ^{13}C-NMR (C_5D_5N) δ: 17.2, 35.5, 48.4, 50.5, 58.5, 62.8, 116.2, 116.4, 129.8, 136.3, 136.7, 156.98, 157.03. EIMS m/z (%) 302 (M^+, 2), 199 (100). HREIMS m/z M^+: calcd. for $C_{18}H_{22}O_4$, 302.1519; found, 302.1519.

*(2*S*,3*R*)-2-[Bis(4-benzyloxyphenyl)]methyl-3-methyltetramethylene dibenzoate (**30**).* Compound **22** was converted to compound **30** as a colorless oil in 67% yield by the same method as that described for the synthesis of compound **26**, $[\alpha]_D^{20} = -27$ (*c* 1.1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, d, J = 6.9 Hz), 2.27 (1H, m), 3.05 (1H, m), 3.95 (1H, d, J = 12.0 Hz), 4.25 (1H, dd, J = 10.7, 6.5 Hz), 4.30 (1H, dd, J = 10.7, 6.4 Hz), 4.36 (1H, dd, J = 12.0, 3.1 Hz), 4.40 (1H, dd, J = 12.0, 12.0 Hz), 4.91 (2H, s), 4.97 (2H, s), 6.83 (2H, d, J = 8.9 Hz), 6.85 (2H, d, J = 8.7 Hz), 7.24–7.47 (18H, m), 7.51–7.56 (2H, m), 7.96–8.05 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 11.3, 32.6, 41.2, 51.0, 63.8, 68.8, 69.88, 69.94, 115.1, 127.4, 127.9, 128.4, 128.5, 128.7, 129.4, 129.5, 130.0, 130.3, 132.9, 135.67, 135.73, 136.96, 136.98, 157.4, 166.2, 166.3. FABMS m/z (%): 691 [$(M + H)^+$, 2.2], 154 (100), 136 (67). HRFABMS m/z $(M + H)^+$: calcd. for $C_{46}H_{43}O_6$, 691.3059; found, 691.3057.

*(2*S*,3*R*)-2-[Bis(4-hydroxyphenyl)]methyl-3-methyl-1,4-butanediol (**31**).* Compound **30** was converted to compound **31** as a colorless oil in 56% yield through 2 steps by the same method as that described for the synthesis of **29**, $[\alpha]_D^{20} = -9$ (*c* 0.2, MeOH). ^{1}H-NMR (CD_3OD) δ: 0.88 (3H, d, J = 7.1 Hz), 1.81 (1H, m), 2.56 (1H, m), 3.42 (2H, d, J = 5.4 Hz), 3.56 (2H, d, J = 5.6 Hz), 3.60 (1H, d, J = 12.1 Hz), 6.66–6.68 (4H, m), 7.12–7.16 (4H, m). ^{13}C-NMR (CD_3OD) δ: 11.6, 37.5, 48.1, 53.1, 62.3, 69.3, 117.06, 117.08, 130.5, 130.7, 137.7, 138.2, 157.3. FABMS m/z (%): 303 [$(M + 1)^+$, 12], 154 (100), 136 (68). HRFABMS m/z $(M + H)^+$: calcd. for $C_{18}H_{23}O_4$, 303.1597; found, 303.1595.

*(*R*)-3-[Bis(4-benzyloxyphenyl)]methyl-4-butanolide (**32**).* Compound **23** was converted to compound **32** as colorless crystals, mp 154–155 °C (EtOAc), in 65% yield by the same method as that described for the synthesis of compound **26**, $[\alpha]_D^{20} = -3$ (*c* 1.3, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.22 (1H, dd, J = 17.8, 8.0 Hz), 2.52 (1H, dd, J = 17.8, 8.3 Hz), 3.30 (1H, m), 3.69 (1H, d, J = 11.5 Hz), 3.93 (1H, dd, J = 9.4, 7.0 Hz), 4.22 (1H, dd, J = 9.4, 7.4 Hz), 4.99 (4H, s), 6.87–6.91 (4H, m), 7.11–7.14 (4H, m), 7.29–7.41 (10H, m). ^{13}C-NMR ($CDCl_3$) δ: 34.0, 40.1, 53.7, 70.0, 72.2, 115.1, 115.2, 127.4, 127.9, 128.39, 128.41, 128.5, 134.5, 135.0, 136.80, 136.83, 157.6, 157.7, 176.6. *Anal*. Found: C, 79.95%; H, 6.10%. Calcd. for $C_{31}H_{28}O_4$: C, 80.15%; H, 6.08%.

*(2*S*,3*S*)-3-[Bis(4-benzyloxyphenyl)]methyl-2-methyl-4-butanolide (**33**).* Compound **32** was converted to compound **33** as colorless crystals, mp 125–126 °C (MeOH), in 75% yield by the same method as that described for the synthesis of compound **13**, $[\alpha]_D^{20} = +14$ (*c* 1.4, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, d, J = 7.3 Hz), 2.32 (1H, m), 2.93 (1H, m), 3.69 (1H, d, J = 11.2 Hz), 3.76 (1H, dd, J = 9.5, 8.4 Hz), 4.25 (1H, dd, J = 9.5, 7.8 Hz), 5.00 (4H, s), 6.85–6.91 (4H, m), 7.13–7.18 (4H, m), 7.25–7.41 (10H, m). ^{13}C-NMR ($CDCl_3$) δ: 15.5, 40.3, 47.4, 54.7, 69.95, 70.00, 115.19, 115.21, 127.4, 128.0, 128.4, 128.52, 128.54, 128.6, 134.3, 135.0, 136.82, 136.84, 157.7, 179.8. FABMS m/z (%): 479 [$(M + H)^+$, 5], 154 (100), 136 (66). HRFABMS m/z $(M + H)^+$: calcd. for $C_{32}H_{31}O_4$, 479.2222; found, 479.2224.

*(2*S*,3*S*)-3-[Bis(4-hydroxyphenyl)]methyl-2-methyl-4-butanolide (**34**).* A reaction mixture of **33** (0.38 g, 0.79 mmol) and 5% Pd/C (0.57 g) in THF (10 ml) was stirred under H_2 gas at the ambient temperature for

6 h before filtration. After the filtrate was concentrated, the residue was applied to silica gel column chromatography (EtOAc:hexane = 1:1) to give **34** (0.14 g, 0.47 mmol, 59%) as colorless crystals, mp 105–106 °C (EtOAc), $[\alpha]_D^{20} = +21$ (*c* 0.6, MeOH). ^{1}H-NMR (C_5D_5N) δ: 0.96 (3H, d, $J = 7.2$ Hz), 2.55 (1H, m), 3.13 (1H, m), 3.85 (1H, dd, $J = 8.9$, 8.1 Hz), 3.88 (1H, d, $J = 11.2$ Hz), 4.34 (1H, dd, $J = 8.9$, 8.1 Hz), 7.13–7.25 (4H, m), 7.33–7.41 (4H, m). ^{13}C-NMR (C_5D_5N) δ: 22.8, 40.5, 47.4, 55.0, 70.8, 116.2, 116.3, 116.39, 116.43, 129.1, 129.3, 133.8, 134.5, 157.5, 179.9. FABMS *m/z* (%): 299 [$(M + 1)^+$, 13], 154 (100), 136 (70). HRFABMS *m/z* $(M + H)^+$: calcd. for $C_{18}H_{19}O_4$, 299.1284; found, 299.1284.

*(2*R*,3*S*)-3-[Bis(4-hydroxyphenyl)]methyl-2-methyl-4-butanolide (**35**).* A reaction mixture of **24** (0.44 g, 1.41 mmol), benzyloxybenzene (1.30 g, 7.06 mmol), and $[Ir_2(COD)_2(SnCl_3)_2(Cl)_2(\mu\text{-}Cl)_2]$ (12 mg, 0.01 mmol) in $Cl(CH_2)_2Cl$ (4 ml) was stirred at 80 °C for 12 h before addition of a few drops of Et_3N and concentration. The residue was applied to silica gel column chromatography (EtOAc:hexane = 1:1) to give Friedel-Crafts product (0.40 g) as a mixture with impurity. A reaction mixture of the Friedel-Crafts product (0.40 g) with impurity and 5% Pd/C (0.62 g) in THF (10 ml) was stirred under H_2 gas at the ambient temperature for 6 h before filtration. After concentration of the filtrate, the residue was applied to silica gel column chromatography (EtOAc:hexane = 1:1) to give **35** (0.24 mmol, 0.80 mmol, 57%) as colorless crystals, mp 89–90 °C, $[\alpha]_D^{20} = -35$ (*c* 0.3, MeOH). ^{1}H-NMR (C_5D_5N) δ: 1.17 (3H, d, $J = 7.7$ Hz), 2.83 (1H, m), 3.62 (1H, m), 4.00 (1H, d, $J = 12.0$ Hz), 4.11 (2H, d, $J = 10.3$ Hz), 5.03 (2H, br. s), 7.14–7.21 (4H, m), 7.33–7.43 (4H, m). ^{13}C-NMR (C_5D_5N) δ: 10.5, 37.6, 43.2, 49.0, 71.0, 116.6, 128.9, 129.0, 134.2, 134.3, 157.6, 157.7, 180.5. EIMS *m/z* (%): 298 (M^+, 5), 199 (100). HREIMS *m/z* M^+: calcd. for $C_{18}H_{18}O_4$, 298.1205; found, 298.1207.

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