Bioscience, Biotechnology, and Biochemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/tbbb20

First Stereoselective Synthesis of (+)-Magnostellin C, a Tetrahydrofuran Type of Lignan Bearing a Chiral Secondary Benzyl Alcohol

Satoshi YAMAUCHI[a] & Yoshiro KINOSHITA[a]
[a] College of Agriculture, Ehime University
Published online: 22 May 2014.

To cite this article: Satoshi YAMAUCHI & Yoshiro KINOSHITA (2001) First Stereoselective Synthesis of (+)-Magnostellin C, a Tetrahydrofuran Type of Lignan Bearing a Chiral Secondary Benzyl Alcohol, Bioscience, Biotechnology, and Biochemistry, 65:7, 1559-1567, DOI: 10.1271/bbb.65.1559

To link to this article: http://dx.doi.org/10.1271/bbb.65.1559

Biosci. Biotechnol. Biochem., **65** (7), 1559–1567, 2001

First Stereoselective Synthesis of (+)-Magnostellin C, a Tetrahydrofuran Type of Lignan Bearing a Chiral Secondary Benzyl Alcohol

Satoshi YAMAUCHI† and Yoshiro KINOSHITA

College of Agriculture, Ehime University, Tarumi 3-5-7, Matsuyama, Ehime 790-8566, Japan

Received January 15, 2001; Accepted February 23, 2001

(+)-Magnostellin C, which is a tetrahydrofuran type of lignan bearing a chiral secondary benzylic hydroxy group, was stereoselectively synthesized from L-arabinose by using *threo* selective aldol condensation.

Key words: lignan; tetrahydrofuran lignan; Magnostellin

Results and discussion

(+)-Magnostellin C (**1**) has been isolated from *Virola elongata*[1] which is used as hallucinogenic snuff. Magnostellins are of the tetrahydrofuran type of lignans bearing a chiral secondary benzyl alcohol. Tetrahydrofuran lignans are known as a PAF inhibitor and stress compound in plants.[2] There have been no reports of any detailed studies on the biological activity and synthesis of magnostellins, although the activity of oxidized tetrahydrofuran lignan and stereoselective introduction of a benzylic hydroxy group are interesting topics. This present report describes the first stereoselective synthesis of (+)-magnostellin C (**1**).

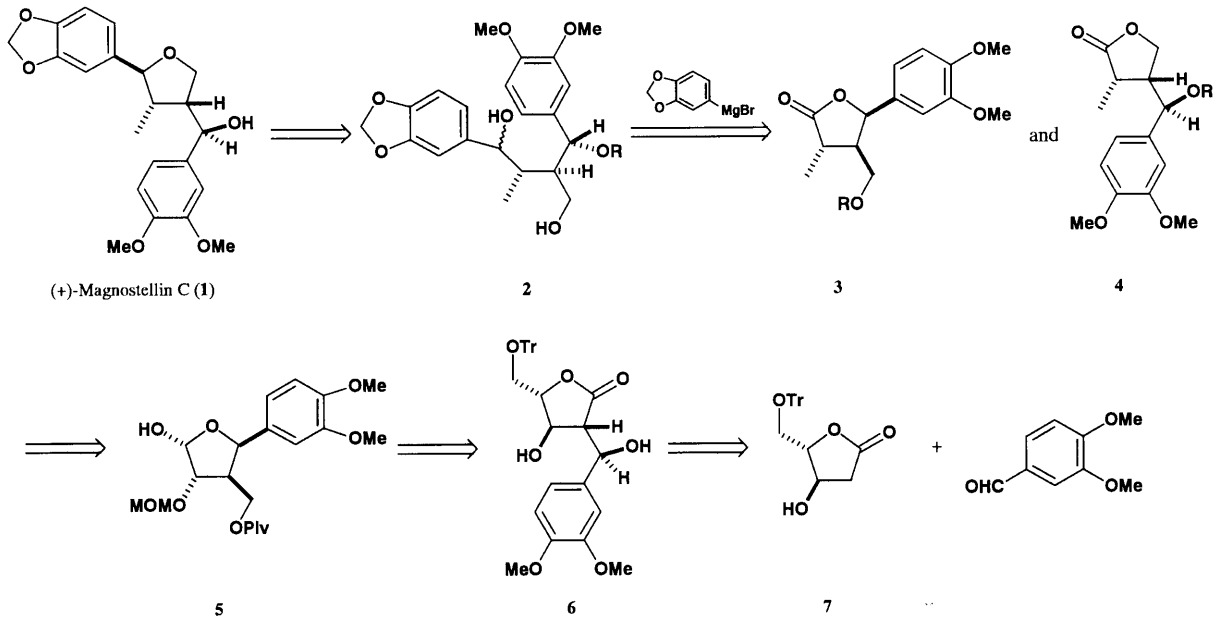
The retrosynthetic plan to (+)-magnostellin C (**1**) is presented in scheme 1. The tetrahydrofuran ring of (+)-magnostellin C might arise by stereoconvergent SN1 ring closure[3] of diol **2**. Lactones **3** and **4** would be converted to diol **2** by a few steps involving reduction and introduction of the 3,4-methylenedioxyphenyl group. These lactones **3** and **4** would be obtained from hemiacetal **5** by oxidation, radical deoxygenation, stereoselective methylation, and hydrolysis. If the aldol condensation of pentanolide **7** with 3,4-dimethoxybenzaldehyde could give high *threo* selectivity to stereoselectively produce aldol product **6**, like the case of the aldol condensation between pentanolide **7** and piperonal,[4] aldol product **6** could be transformed to hemiacetal **5** by the previously described method.[4] The benzylic position of aldol product **6** would be transformed to a benzylic position bearing the hydroxy group of (+)-magnostellin C (**1**).

As expected, the aldol condensation of pentanolide **7**[4] with 3,4-dimethoxybenzaldehyde proceeded *threo* preferentially (*erythro:threo* = 1:9) to give aldol product **6** in 60% yield. Hemiacetal **5** was obtained from **6** in 6 steps with 21% overall yield by the previously described method[4] (Scheme 2).

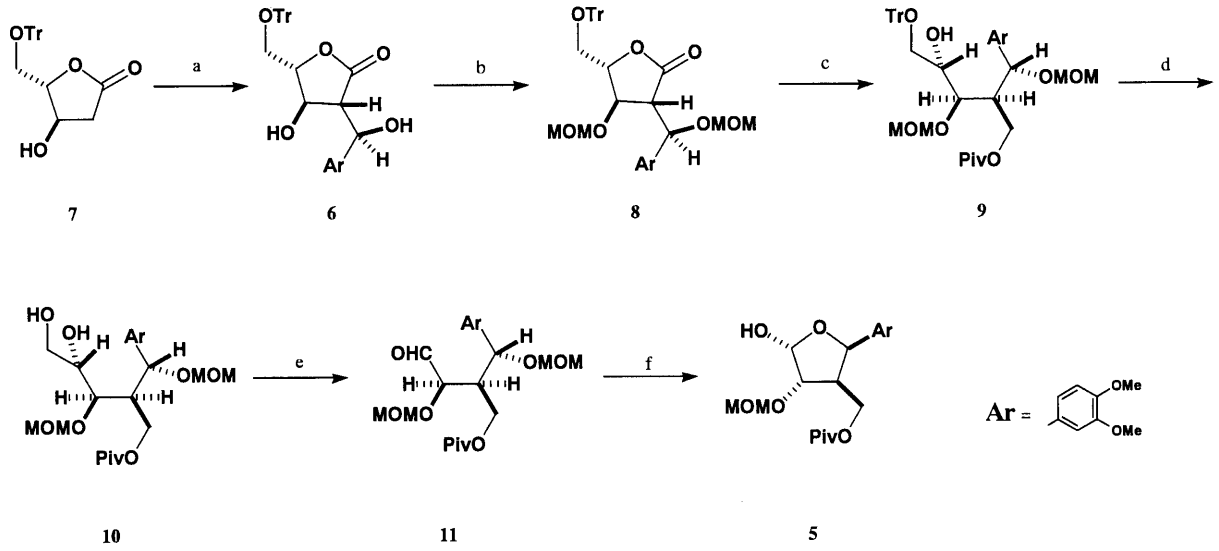
After pyridinium chlorochromate oxidation of hemiacetal **5** (83% yield), cleavage of the methoxymethyl ether with a 6 M aqueous HCl solution was performed to afford hydroxy lactone **13** in 74% yield. No NOE relationship between H-4 and the methylene protons of the pivaloyloxymethyl group was apparent. This fact suggested that no epimerization at the benzylic position (4 position) had occurred under these acidic conditions for demethoxymethylation. Hydroxy lactone **13** was converted to thionoformate **14** by using phenyl chlorothionoformate, pyridine, and 4-dimethylaminopyridine in 82% yield, **14** then being subjected to radical deoxygenation by being treated with tri(*n*-butyl)tin hydride and 2,2′-azobis(isobutyronitrile), giving *cis*-butyrolactone **15** in quantitative yield. *cis*-Butyrolactone **15** might be useful for stereoselective alkylation to the α position. Methyl lactone **16** was obtained by stereoselective methylation of *cis*-butyrolactone **15** with lithium bis(trimethylsilyl)amide and methyl iodide in 88% yield. Cleavage of the pivaloyl ester of **16** under alkaline conditions gave lactone **17** (55%) and lactone **18** (37%). A NOE experiment on **17** revealed correlation of the methylene protons of the hydroxymethyl group at the 3 position with aromatic protons and 2-*H*. The transformation of both lactone **17** and **18** to (+)-magnostellin C was then respectively attempted.

After protecting the hydroxy group of **17** as a *tert*-butyldiphenylsilyl ether with *tert*-butylchlorodiphenylsilane and imidazole in 88% yield, silyloxy lactone **19** was subjected to reduction by diisobutylaluminum hydride and sodium borohydride. Without purification, the resulting diol was exposed to a reaction with pivaloyl chloride to give **20** in 90% yield from **19**. Direct $LiAlH_4$ reduction of **19** caused desilylation. Treatment of **20** with chloromethyl methyl ether in the presence of *N*,*N*-diisopropylethylamine and subsequent diisobutylalu-

† To whom correspondence should be addressed. Fax: +81-89-977-4364; E-mail: syamauch@agr.ehime-u.ac.jp



Scheme 1. Retrosynthetic Analysis of (+)-Magnostellin C.



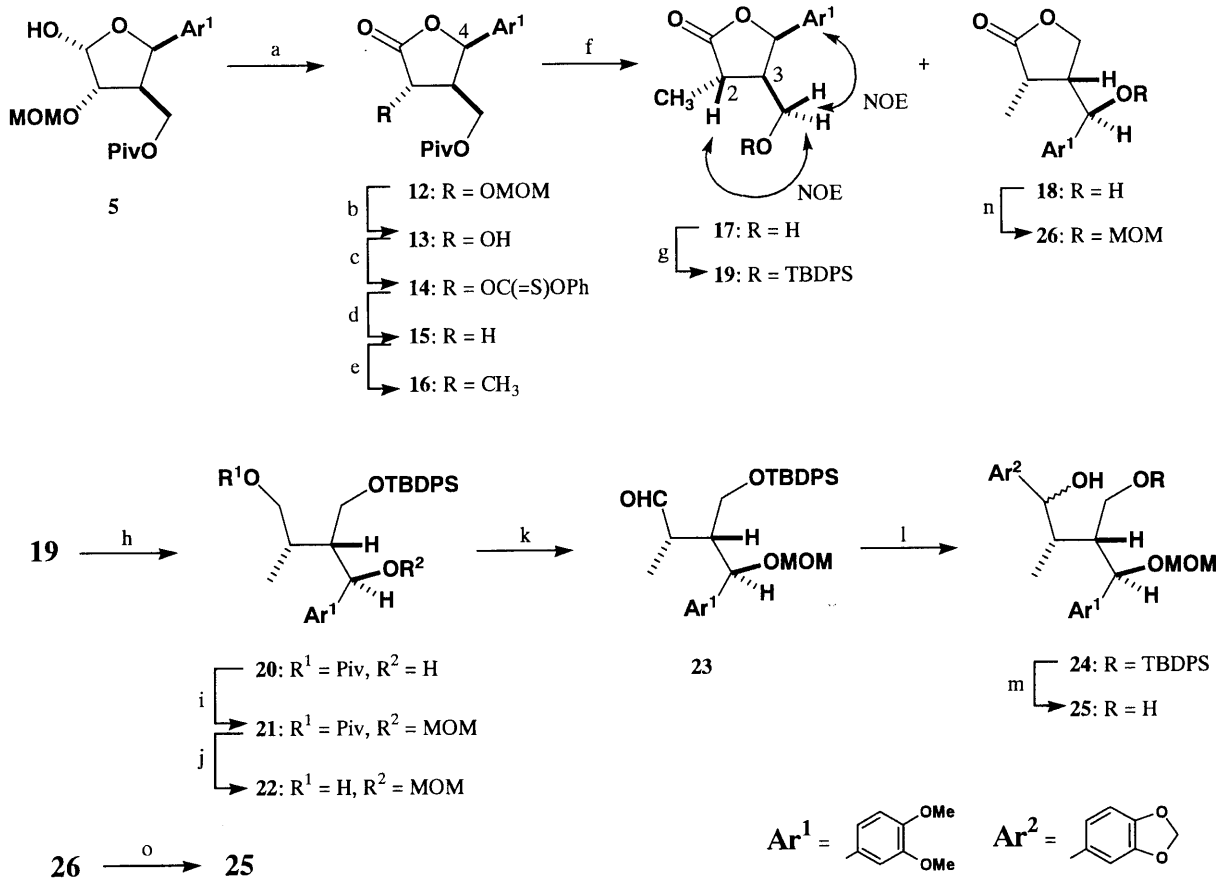
Scheme 2. Synthesis of (+)-Magnostellin C (1).

(a) LDA, 3,4-dimethoxybenzaldehyde, THF, −75°C, 1 h (60% yield). (b) MOMCl, $(i\text{-Pr})_2$EtN, CH_2Cl_2, r.t., 3 h (81% yield). (c) (1) $LiAlH_4$, THF, r.t., 30 min; (2) PivCl, pyridine, r.t., 1 h (83% yield, 2 steps). (d) PPTS, MeOH, reflux, 3 h (80% yield). (e) $NaIO_4$, MeOH, r.t., 3 h (89% yield). (f) PPTS, *tert*-butyl alcohol, reflux, 2 h (74% yield).

minum hydride reduction provided alcohol **22** in 86% yield from **20**. Pyridinium chlorochromate oxidation of alcohol **22** afforded aldehyde **23** in 90% yield, this being treated with 3,4-methylenedioxyphenylmagnesium bromide, leading to an inseparable 1:1 mixture of benzyl alcohol **24** in 89% yield. Having a synthetic plan for SN1 ring closure to the tetrahydrofuran ring, high stereoselectivity in this stage was not necessary. Cleavage of the silyl ether of **24** with tetrabutylammonium fluoride gave diol **25** in 88 % yield. This was a substrate for ring closure to the tetrahydrofuran ring.

The conversion of lactone **18** to diol **25** was also successful. After the hydroxy group of **18** had been protected as a methoxymethyl ether by using chloromethyl methyl ether and *N*,*N*-diisopropylethylamine in 87% yield, resulting lactone **26** was reduced to the corresponding hemiacetal by diisobutylaluminum hydride. Without purification, this hemiacetal was reacted with 3,4-methylenedioxyphenylmagnesium bromide to give diol **25** as a 1:1 mixture of diastereomers in 87% yield (Scheme 3).

The acid-induced SN1 type of cyclization of diol **25** was carefully conducted by using a catalytic amount of 10-camphorsulfonic acid in dichloromethane at 0°C, giving protected magnostellin C (**27**) in 63%



Scheme 3. Synthesis of (+)-Magnostellin C (2).

(a) PCC, MS 4A, CH_2Cl_2, r.t., 40 h (83% yield). (b) 6 M aq. HCl, THF, r.t., 30 min (74% yield). (c) PhOC(=S)Cl, pyridine, DMAP, MeCN, r.t., 30 min (82% yield). (d) $(n\text{-Bu})_3SnH$, AIBN, toluene, reflux, 30 min (100% yield). (e) MeI, LHMDS, THF, −75°C, 30 min (88% yield). (f) 1 M aq. NaOH, EtOH, r.t., 16 h, and then 1 M aq. HCl soln. (**17**: 55% yield. **18**: 37% yield). (g) TBDPSCl, imidazole, DMF, r.t., 16 h (88% yield). (h) (1) DIBAL-H, toluene, −75°C, 30 min; (2) $NaBH_4$, EtOH, r.t., 1 h; (3) PivCl, pyridine, 0°C, 1 h (90% yield, 3 steps). (i) MOMCl, $(i\text{-Pr})_2EtN$, CH_2Cl_2, r.t., 15 h (93% yield). (j) DIBAL-H, −75°C, 30 min (92% yield). (k) PCC, MS 4A, CH_2Cl_2, r.t., 1 h (90% yield). (l) 3,4-methylenedioxyphenylmagnesium bromide, THF, 0°C, 1 h (89% yield). (m) $(n\text{-Bu})_4NF$, THF, 0°C, 1 h (88% yield). (n) MOMCl, $(i\text{-Pr})_2EtN$, CH_2Cl_2, r.t., 48 h (87% yield). (o) (1) DIBAL-H, toluene, −75°C, 30 min; (2) 3,4-methylenedioxyphenylmagnesium bromide, THF, reflux, 20 h (87% yield, 2 steps).

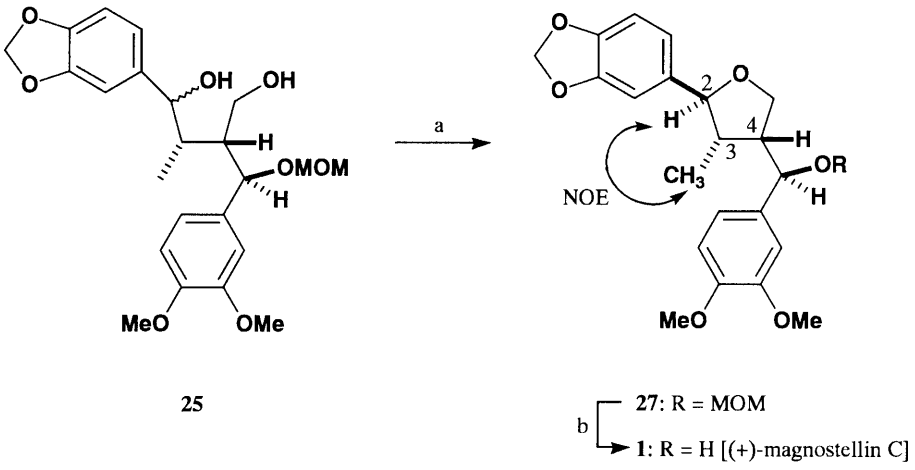
yield. Any higher temperature caused intramolecular etherificaion between the two benzylic positions due to the production of the 3,4-dimethoxybenzylic cation, but the lower temperature could avoid the production of this cation. Finally, cleavage of the methoxymethyl ether of **27** was performed by treating with bromotrimethylsilane[5] to provide (+)-magnostellin C (**1**) in 55% yield. The exposure of **27** to a diluted aqueous HCl solution resulted in the production of many unidentified compounds. No epimerization at the benzylic position bearing a secondary hydroxy group was apparent in this reaction. This fact was confirmed by converting the obtained (+)-magnostellin C (**1**) to **27** by methoxymethylation. The existence of NOE between the methyl protons and benzylic proton at the 2 position and no NOE existing between the methyl protons and 4-H revealed the configurations of the 2, 3 and 4 positions (Scheme 4). The NMR data for synthesized (+)-magnostellin C are almost in agreement with the data described in the literature.[1]

The first synthesis of (+)-magnostellin C (**1**) was stereoselectively achieved from L-arabinose in 22–28 steps with 0.7–1.0% overall yield by using *threo*-selective aldol condensation as key step. The benzylic position of the *threo* aldol product was converted to a benzylic position bearing the hydroxy group of (+)-magnostellin C.

Experimental

All melting point (mp) data are uncorrected. NMR data were measured by a JNM-EX400 spectrometer, EIMS data were measured with a Hitachi M-80B spectrometer, and optical rotation values were evaluated with a HORIBA SEPA-200 instrument. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh), and preparative TLC was done with Merck silica gel 60 F_{254} (0.5 mm thickness, 20×20 cm).

(2R,3R,4S)-3-Hydroxy-2-[(1R)-1-hydroxy-1-(3,4-dimethoxyphenyl)methyl-5-trityloxy-4-pentanolide



Scheme 4. Synthesis of (+)-Magnostellin C (3).
(a) CSA, CH_2Cl_2, 0°C, 16 h (63% yield). (b) TMSBr, CH_2Cl_2, 0°C, 30 min (55% yield).

(**6**). Colorless crystals, mp 154–155°C (EtOAc/*i*-Pr_2O = 1/2), $[\alpha]_D^{20} = -39$ (*c* 0.62, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.43 (1H, d, *J* = 2.9 Hz), 2.96 (1H, dd, *J* = 8.3, 8.3 Hz), 3.20 (1H, dd, *J* = 10.7, 4.4 Hz), 3.48 (1H, dd, *J* = 10.7, 2.9 Hz), 3.84 (3H, s), 3.85 (3H, s), 3.99 (1H, s), 4.15 (1H, m), 4.25 (1H, m), 4.89 (1H, dd, *J* = 8.3, 2.9 Hz), 6.82 (1H, d, *J* = 8.3 Hz), 6.87 (1H, dd, *J* = 8.3, 2.0 Hz), 6.95 (1H, d, *J* = 2.0 Hz), 7.22–7.32 (9H, m), 7.38–7.41 (6H, m). NMR δ_C ($CDCl_3$): 55.3, 55.9, 62.1, 70.0, 73.3, 82.7, 87.0, 109.6, 111.1, 118.8, 127.3, 127.9, 128.5, 131.9, 143.3, 149.3, 149.5, 175.7. IR ν_{max} ($CHCl_3$): 3594, 2938, 1763, 1518, 1266, 1238, 1174, 1156, 1140, 1044, 1028 cm^{-1}. EIMS *m/z* (20 eV): 540 (M^+, 0.5), 243 (100), 165 (75), 105 (63). *Anal.* Found: C, 73.09; H, 6.05%. Calcd. for $C_{33}H_{32}O_7$: C, 73.32; H, 5.97%.

(2R,3R,4S)-3-Methoxymethoxy-2-[(1R)-1-methoxymethoxy-1-(3,4-dimethoxyphenyl)methyl-5-trityloxy-4-pentanolide (**8**). Colorless oil, $[\alpha]_D^{20} = +4.2$ (*c* 2.40, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.85 (1H, dd, *J* = 10.5, 5.1 Hz), 3.08 (1H, dd, *J* = 10.5, 3.4 Hz), 3.11 (3H, s), 3.19 (1H, dd, *J* = 5.4, 4.4 Hz), 3.36 (3H, s), 3.78 (3H, s), 3.79 (3H, s), 4.25–4.30 (2H, m), 4.40 (1H, d, *J* = 6.8 Hz), 4.44 (1H, d, *J* = 6.8 Hz), 4.59 (2H, s), 5.15 (1H, d, *J* = 4.4 Hz), 6.63 (1H, d, *J* = 8.3 Hz), 6.81 (1H, d, *J* = 8.3 Hz), 6.92 (1H, s), 7.21–7.36 (10H, m), 7.47–7.48 (5H, m). NMR δ_C ($CDCl_3$): 54.2, 55.4, 55.7, 55.8, 55.9, 62.7, 74.7, 82.6, 86.9, 94.2, 95.6, 110.4, 110.8, 120.0, 127.1, 127.8, 128.6, 129.7, 143.4, 148.8, 148.9, 173.5. IR ν_{max} ($CHCl_3$): 2938, 1775, 1518, 1466, 1451, 1443, 1262, 1235, 1154, 1105, 1071, 1028 cm^{-1}. EIMS *m/z* (20 eV): 628 (M^+, 2), 243 (100). *Anal.* Found: C, 70.52; H, 6.51%. Calcd. for $C_{37}H_{40}O_9$: C, 70.68; H, 6.41%.

(2S,3R,4R,5R)-3,5-Bis(methoxymethoxy)-5-(3,4-dimethoxyphenyl)-4-pivaloyloxymethyl-1-trityloxy-2-pentanol (**9**). Colorless oil, $[\alpha]_D^{20} = +57$ (*c* 0.54, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.21 (9H, s), 2.56 (1H, m), 2.65 (1H, d, *J* = 7.3 Hz), 3.08 (1H, dd, *J* = 9.8, 4.9 Hz), 3.15 (3H, s), 3.31 (3H, s), 3.31–3.34 (1H, m), 3.61 (1H, dd, *J* = 7.8, 3.9 Hz), 3.74 (1H, m), 3.83 (3H, s), 3.85 (3H, s), 4.26 (1H, d, *J* = 6.8 Hz), 4.32 (1H, d, *J* = 6.8 Hz), 4.42–4.49 (4H, m), 4.95 (1H, d, *J* = 7.8 Hz), 6.78 (1H, d, *J* = 8.3 Hz), 6.88 (1H, dd, *J* = 8.3, 2.0 Hz), 6.92 (1H, d, *J* = 2.0 Hz), 7.19–7.29 (10H, m), 7.31–7.34 (5H, m). NMR δ_C ($CDCl_3$): 27.2, 38.8, 46.8, 55.8, 56.0, 61.6, 64.4, 70.8, 76.2, 79.2, 86.6, 94.3, 98.0, 110.4, 110.7, 120.5, 127.1, 127.8, 127.9, 128.6, 132.8, 143.7, 148.5, 149.1, 178.3. IR ν_{max} ($CHCl_3$): 3577, 2938, 1721, 1516, 1466, 1449, 1287, 1262, 1233, 1161, 1142, 1100, 1057, 1030 cm^{-1}. EIMS *m/z* (20 eV): 699 (M^+-OH, 1.3), 243 (100), 211 (77). *Anal.* Found: C, 71.04; H, 7.35%. Calcd. for $C_{42}H_{52}O_{10}$: C, 70.37; H, 7.31%.

(2S,3R,4R,5R)-3,5-Bis(methoxymethoxy)-5-(3,4-dimethoxyphenyl)-4-pivaloyloxymethyl-1,2-pentanediol (**10**). Colorless oil, $[\alpha]_D^{20} = +49$ (*c* 2.00, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.19 (9H, s), 2.28–2.38 (2H, m), 3.25 (1H, d, *J* = 7.3 Hz), 3.35 (3H, s), 3.40 (3H, s), 3.60–3.69 (4H, m), 3.88 (3H, s), 3.89 (3H, s), 4.33 (1H, dd, *J* = 9.6, 6.4 Hz), 4.38 (1H, dd, *J* = 9.6, 3.2 Hz), 4.49 (2H, s), 4.60 (1H, d, *J* = 6.6 Hz), 4.63 (1H, d, *J* = 6.6 Hz), 4.92 (1H, d, *J* = 6.3 Hz), 6.80–6.88 (3H, m). NMR δ_C ($CDCl_3$): 27.1, 38.7, 47.1, 55.8, 55.9, 56.1, 56.2, 61.2, 63.4, 71.4, 76.2, 81.0, 94.7, 98.4, 110.1, 110.9, 119.9, 132.4, 148.6, 149.1, 178.2. IR ν_{max} ($CHCl_3$): 3410, 2961, 1721, 1516, 1466, 1285, 1262, 1237, 1159, 1142, 1096, 1073, 1028 cm^{-1}. EIMS *m/z* (20 eV): 474 (M^+, 78), 295 (57), 212 (100), 165 (99). *Anal.* Found: C, 57.98; H, 8.07%. Calcd. for $C_{23}H_{38}O_{10}$: C, 58.21; H, 8.07%.

(2R,3R,4R)-2,4-Bis(methoxymethoxy)-4-(3,4-dimethoxyphenyl)-3-pivaloyloxymethylbutanal (**11**).

Colorless oil, $[\alpha]_D^{20} = +95$ (*c* 1.19, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.21 (9H, s), 2.71 (1H, m), 3.32 (3H, s), 3.35 (3H, s), 3.85 (1H, dd, *J* = 2.0, 1.5 Hz), 3.88 (6H, s), 4.33 (1H, dd, *J* = 11.1, 8.1 Hz), 4.42 (1H, d, *J* = 6.6 Hz), 4.45 (1H, d, *J* = 6.6 Hz), 4.56 (1H, dd, *J* = 11.1, 3.4 Hz), 4.60 (1H, d, *J* = 7.3 Hz), 4.68 (1H, d, *J* = 7.3 Hz), 4.69 (1H, d, *J* = 9.8 Hz), 6.82 (1H, d, *J* = 7.8 Hz), 6.89 (1H, d, *J* = 2.0 Hz), 6.94 (1H, dd, *J* = 7.8, 2.0 Hz), 9.01 (1H, d, *J* = 1.5 Hz). NMR δ_C ($CDCl_3$): 27.1, 38.8, 49.2, 55.8, 56.0, 56.1, 61.4, 74.3, 80.7, 93.9, 97.5, 110.7, 111.0, 121.3, 130.8, 149.2, 149.3, 178.2, 201.9. IR ν_{max} ($CHCl_3$): 2938, 1727, 1516, 1466, 1283, 1264, 1161, 1028 cm^{-1}. EIMS *m/z* (20 eV): 442 (M^+, 99), 212 (100), 181 (99), 165 (99). *Anal.* Found: C, 59.52; H, 7.73%. Calcd. for $C_{22}H_{34}O_9$: C, 59.71; H, 7.74%.

(2R,3S,4R,5R)-2-Hydroxy-3-methoxymethoxy-5-(3,4-dimethoxyphenyl)-4-pivaloyloxymethyltetrahydrofuran (**5**). Colorless oil, $[\alpha]_D^{20} = -26$ (*c* 0.96, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.13 (9H, s), 3.13 (1H, m), 3.41 (3H, s), 3.75–3.80 (2H, m), 3.86 (6H, s), 4.14 (1H, d, *J* = 5.4 Hz), 4.70 (1H, d, *J* = 6.8 Hz), 4.75 (1H, d, *J* = 6.8 Hz), 5.32 (1H, d, *J* = 9.3 Hz), 5.64 (1H, d, *J* = 2.4 Hz), 6.78 (1H, d, *J* = 8.3 Hz), 6.86 (1H, dd, *J* = 8.3, 2.0 Hz), 7.04 (1H, d, *J* = 2.0 Hz). NMR δ_C ($CDCl_3$): 27.1, 38.5, 42.8, 55.6, 55.7, 55.8, 60.4, 81.3, 81.9, 97.0, 100.6, 110.4, 110.8, 120.0, 130.5, 148.6, 178.1. IR ν_{max} ($CHCl_3$): 3602, 2961, 1723, 1518, 1466, 1283, 1266, 1235, 1165, 1144, 1030 cm^{-1}. EIMS *m/z* (20 eV): 398 (M^+, 24), 167 (100). *Anal.* Found: C, 59.95; H, 7.62%. Calcd. for $C_{20}H_{30}O_8$: C, 60.29; H, 7.59%.

(2S,3R,4R)-2-Methoxymethoxy-4-(3,4-dimethoxyphenyl)-3-pivaloyloxymethyl-4-butanolide (**12**). A reaction mixture of hemiacetal **5** (2.63 g, 6.60 mmol), pyridinium chlorochromate (1.54 g, 7.14 mmol), and 4A molecular sieves (0.20 g) in CH_2Cl_2 (50 ml) was stirred at room temperature for 40 h before adding ether. After filtration, the filtrate was concentrated. The residue was applied to silica gel column chromatography (20% EtOAc/benzene) to give lactone **12** (2.17 g, 5.47 mmol, 83%) as a colorless oil, $[\alpha]_D^{20} = +65$ (*c* 1.24, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.15 (9H, s), 3.10 (1H, m), 3.46 (3H, s), 3.69 (1H, dd, *J* = 11.7, 2.4 Hz), 3.86 (3H, s), 3.89 (3H, s), 4.22 (1H, dd, *J* = 11.7, 3.9 Hz), 4.75 (1H, d, *J* = 6.8 Hz), 4.76 (1H, d, *J* = 7.8 Hz), 5.01 (1H, d, *J* = 6.8 Hz), 5.57 (1H, d, *J* = 5.9 Hz), 6.87 (3H, s). NMR δ_C ($CDCl_3$): 26.9, 38.5, 43.9, 55.9, 56.0, 56.2, 58.8, 71.7, 78.8, 96.4, 108.5, 111.1, 117.9, 126.9, 149.0, 149.2, 173.9, 177.9. IR ν_{max} ($CHCl_3$): 2967, 1792, 1727, 1520, 1466, 1271, 1260, 1156, 1051, 1028 cm^{-1}. EIMS *m/z* (20 eV): 396 (M^+, 82), 177 (100). *Anal.* Found: C, 60.33; H, 7.11%. Calcd. for $C_{20}H_{28}O_8$: C, 60.59; H, 7.12%.

(2S,3S,4R)-2-Hydroxy-4-(3,4-dimethoxyphenyl)-3-pivaloyloxymethyl-4-butanolide (**13**). After a reaction solution of methoxymethyl ether **12** (2.09 g, 5.27 mmol) in a 6 M aq. HCl soln. (30 ml) and THF (30 ml) had been stirred at room temperature for 30 min, EtOAc and H_2O were added. The organic solution was separated, successively washed with a sat. aq. $NaHCO_3$ soln. and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 2/1) gave alcohol **13** (1.37 g, 3.89 mmol, 74%) as colorless crystals, mp 118–120°C (EtOH/*i*-Pr_2O = 1/3), $[\alpha]_D^{20} = +69$ (*c* 0.32, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.14 (9H, s), 3.12 (1H, m), 3.20 (1H, d, *J* = 4.4 Hz), 3.76 (1H, dd, *J* = 11.7, 2.4 Hz), 3.87 (3H, s), 3.89 (3H, s), 4.25 (1H, dd, *J* = 11.7, 3.7 Hz), 4.82 (1H, dd, *J* = 7.8, 4.4 Hz), 5.61 (1H, d, *J* = 5.9 Hz), 6.86–6.88 (3H, m). NMR δ_C ($CDCl_3$): 26.9, 38.5, 44.8, 55.9, 56.0, 58.6, 69.3, 79.0, 108.4, 111.2, 117.7, 126.6, 149.1, 149.2, 176.4, 178.0. IR ν_{max} ($CHCl_3$): 3569, 2973, 1790, 1728, 1520, 1464, 1271, 1260, 1183, 1161, 1146 cm^{-1}. EIMS *m/z* (20 eV): 352 (M^+, 71), 167 (100). *Anal.* Found: C, 61.29; H, 6.93%. Calcd. for $C_{18}H_{24}O_7$: C, 61.35; H, 6.87%.

(2S,3R,4R)-4-(3,4-Dimethoxyphenyl)-2-phenoxythiocarbonyloxy-3-pivaloyloxymethyl-4-butanolide (**14**). To an ice-cooled solution of alcohol **13** (1.37 g, 3.89 mmol), 4-dimethylaminopyridine (0.17 g, 1.39 mmol) and pyridine (0.50 ml, 6.18 mmol) in MeCN (30 ml) was added phenyl chlorothionoformate (0.83 ml, 6.00 mmol). After the reaction solution had been stirred at room temperature for 30 min, H_2O and EtOAc were added. The organic solution was separated, successively washed with a 1 M aq. HCl soln., sat. aq. $NaHCO_3$ soln., and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3 and 1/1) gave thionoformate **14** (1.56 g, 3.19 mmol, 82 %) as colorless crystals, mp 135–136°C (benzene/*i*-Pr_2O = 1/1), $[\alpha]_D^{20} = -70$ (*c* 0.40, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.20 (9H, s), 3.52 (1H, m), 3.67 (1H, dd, *J* = 12.2, 1.5 Hz), 3.88 (3H, s), 3.90 (3H, s), 4.18 (1H, dd, *J* = 12.2, 2.9 Hz), 5.74 (1H, d, *J* = 5.4 Hz), 6.28 (1H, d, *J* = 7.8 Hz), 6.90–6.93 (3H, m), 7.14 (2H, d, *J* = 7.3 Hz), 7.30–7.34 (1H, m), 7.42–7.46 (2H, m). NMR δ_C ($CDCl_3$): 26.9, 38.6, 43.0, 55.9, 56.0, 58.3, 76.6, 78.9, 108.4, 111.3, 117.8, 121.5, 125.9, 127.0, 129.7, 149.3, 149.4, 153.5, 170.0, 177.7, 194.4. IR ν_{max} ($CHCl_3$): 2973, 1802, 1730, 1520, 1489, 1464, 1285, 1273, 1224, 1208, 1181, 1161, 1146, 1113, 1026 cm^{-1}. EIMS *m/z* (20 eV): 488 (M^+, 100), 233 (49), 165 (36). *Anal.* Found: C, 61.44; H, 5.95%. Calcd. for $C_{25}H_{28}O_8S$: C, 61.46; H, 5.78%.

(3R,4R)-4-(3,4-Dimethoxyphenyl)-3-pivaloyloxymethyl-4-butanolide (**15**). A reaction solution of thionoformate **14** (1.22 g, 2.50 mmol), tri(*n*-butyl)tin hydride (0.79 ml, 2.94 mmol), and 2,2′-

azobis(isobutyronitrile) (53 mg, 0.32 mmol) in toluene (60 ml) was heated under refluxing for 30 min. After concentration, the residue was applied to silica gel column chromatography (EtOAc/hexane = 1/2 and 2/1) to give lactone **15** (0.84 g, 2.50 mmol, 100%) as colorless crystals, mp 80–81°C (*i*-Pr_2O), $[\alpha]_D^{20} = +48$ (*c* 0.65, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.15 (9H, s), 2.59 (1H, dd, *J* = 17.3, 4.2 Hz), 2.84 (1H, dd, *J* = 17.3, 8.5 Hz), 3.06 (1H, m), 3.65 (1H, dd, *J* = 11.7, 6.3 Hz), 3.88 (1H, dd, *J* = 11.7, 5.4 Hz), 3.88 (6H, s), 5.65 (1H, d, *J* = 6.8 Hz), 6.79 (1H, d, *J* = 1.5 Hz), 6.83 (1H, dd, *J* = 8.3, 2.0 Hz), 6.87 (1H, d, *J* = 8.3 Hz). NMR δ_C ($CDCl_3$): 27.0, 32.5, 38.7, 39.4, 55.9, 56.0, 62.7, 82.1, 108.4, 111.3, 117.7, 127.3, 149.1, 149.3, 175.6, 178.0. IR ν_{max} ($CHCl_3$): 2973, 1782, 1728, 1520, 1466, 1279, 1271, 1260, 1240, 1165, 1144, 1028 cm^{-1}. EIMS *m/z* (20 eV): 336 (M^+, 97), 166 (100). *Anal.* Found: C, 64.22; H, 7.38%. Calcd. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19%.

(2S,3R,4R)-4-(3,4-Dimethoxyphenyl)-2-methyl-3-pivaloyloxymethyl-4-butanolide (**16**). To a solution of lithium bis(trimethylsilyl)amide (1.35 ml, 1 M in THF, 1.35 mmol) in THF (4 ml) was added lactone **15** (0.70 g, 2.08 mmol) in THF (2 ml) at −75°C. After 15 min at −75°C, iodomethane (0.17 ml, 2.73 mmol) was added. The reaction mixture was stirred at −75°C for 30 min before adding a sat. aq. NH_4Cl soln. and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/2) gave methyl lactone **16** (0.64 g, 1.83 mmol, 88%) as colorless crystals, mp 113–114°C (*i*-Pr_2O), $[\alpha]_D^{20} = -55$ (*c* 1.20, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.17 (9H, s), 1.40 (3H, d, *J* = 7.3 Hz), 2.65 (1H, m), 2.79 (1H, m), 3.78–3.83 (2H, m), 3.86 (3H, s), 3.88 (3H, s), 5.63 (1H, d, *J* = 7.3 Hz), 6.71 (1H, s), 6.78 (1H, d, *J* = 8.3 Hz), 6.85 (1H, d, *J* = 8.3 Hz). NMR δ_C ($CDCl_3$): 14.8, 27.1, 36.8, 38.7, 46.7, 55.9, 56.0, 62.9, 80.1, 108.7, 111.2, 118.1, 127.6, 149.2, 177.9, 178.7. IR ν_{max} ($CHCl_3$): 2977, 1775, 1727, 1520, 1464, 1281, 1269, 1260, 1240, 1163, 1146, 1026 cm^{-1}. EIMS *m/z* (20 eV): 350 (M^+, 79), 166 (100). *Anal.* Found: C, 64.94; H, 7.73%. Calcd. for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48%.

(2S,3R,4R)-3-Hydroxymethyl-4-(3,4-dimethoxyphenyl)-2-methyl-4-butanolide (**17**) and *(2S,3R)-3-[(1R)-1-hydroxy-1-(3,4-dimethoxyphenyl)methyl]-2-methyl-4-butanolide* (**18**). A reaction solution of pivaloyl ester **16** (0.64 g, 1.83 mmol) in a 1 M aq. NaOH soln. (20 ml) and EtOH (20 ml) was stirred at room temperature for 16 h before its acidification with a 1 M aq. HCl soln.. After adding a sat. aq. $NaHCO_3$ soln., 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). Concentration followed by silica gel column chromatography (EtOAc/hexane = 2/1) gave hydroxymethyl lactone **17** (0.27 g, 1.01 mmol, 55%) as a colorless oil and lactone **18** (0.18 g, 0.68 mmol, 37%) as colorless crystals, mp 131–132°C (MeOH). Hydroxymethyl lactone **17**: $[\alpha]_D^{20} = -54$ (*c* 0.24, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.19 (1H, br. s), 1.36 (3H, d, *J* = 6.4 Hz), 2.63–2.66 (2H, m), 3.31–3.38 (1H, m), 3.52 (1H, br. d, *J* = 10.7 Hz), 3.87 (3H, s), 3.89 (3H, s), 5.64 (1H, d, *J* = 7.3 Hz), 6.79 (1H, d, *J* = 1.5 Hz), 6.81 (1H, dd, *J* = 8.3, 1.5 Hz), 6.88 (1H, d, *J* = 8.3 Hz). NMR δ_C ($CDCl_3$): 14.6, 35.7, 49.7, 55.9, 56.0, 61.0, 80.6, 108.9, 111.2, 117.9, 128.3, 149.1, 149.2, 179.4. IR ν_{max} ($CHCl_3$): 3569, 3027, 1771, 1518, 1267, 1260, 1242, 1229, 1173, 1163, 1144, 1026, 1005 cm^{-1}. EIMS *m/z* (20 eV): 266 (M^+, 61), 167 (99). HRMS (EI) *m/z* (M^+): calcd. for $C_{14}H_{18}O_5$, 266.1152; found, 266.1146. Lactone **18**: $[\alpha]_D^{20} = +79$ (*c* 0.24, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.34 (3H, d, *J* = 6.8 Hz), 2.03 (1H, br. s), 2.71 (1H, m), 2.79 (1H, m), 3.88 (3H, s), 3.90 (3H, s), 4.20 (1H, dd, *J* = 9.8, 6.8 Hz), 4.38 (1H, dd, *J* = 9.8, 3.7 Hz), 4.91 (1H, br. s), 6.86–6.91 (3H, m). NMR δ_C ($CDCl_3$): 10.2, 36.6, 45.1, 56.0, 67.2, 71.5, 108.9, 111.3, 118.0, 134.5, 148.8, 149.3, 179.7. IR ν_{max} ($CHCl_3$): 3525, 3023, 1769, 1518, 1264, 1240, 1181, 1156, 1140, 1026 cm^{-1}. EIMS *m/z* (20 eV): 266 (M^+, 44), 167 (99), 139 (100). *Anal.* Found: C, 63.00; H, 6.88%. Calcd. for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81%.

(2S,3R,4R)-3-(tert-Butyldiphenylsilyl)oxymethyl-4-(3,4-dimethoxylphenyl)-2-methyl-4-butanolide (**19**). To a solution of hydroxymethyl lactone **17** (0.27 g, 1.01 mmol) and imidazole (0.15 g, 2.20 mmol) in DMF (1 ml) was added *tert*-butylchlorodiphenylsilane (0.27 ml, 1.04 mmol). The reaction solution was stirred at room temperature for 16 h before adding H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9 and 1/1) gave silyl ether **19** (0.45 g, 0.89 mmol, 88%) as colorless crystals, mp 128–129°C (*iso*-Pr_2O), $[\alpha]_D^{20} = -17$ (*c* 0.47, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.03 (9H, s), 1.18 (3H, d, *J* = 6.8 Hz), 2.51 (1H, m), 2.55 (1H, m), 3.33 (1H, dd, *J* = 10.7, 7.3 Hz), 3.44 (1H, dd, *J* = 10.7, 4.9 Hz), 3.75 (3H, s), 3.88 (3H, s), 5.67 (1H, d, *J* = 7.3 Hz), 6.77–6.79 (2H, m), 6.82 (1H, d, *J* = 8.8 Hz), 7.32–7.36 (5H, m), 7.39–7.43 (2H, m), 7.48–7.50 (3H, m). NMR δ_C ($CDCl_3$): 14.6, 19.1, 26.8, 36.0, 50.2, 55.8, 55.9, 62.3, 80.8, 109.2, 111.0, 118.2, 127.7, 128.3, 129.8, 129.9, 132.8, 132.9, 135.4, 148.9, 149.0, 179.4. IR ν_{max} ($CHCl_3$): 2936, 1771, 1520, 1466, 1428, 1269, 1258, 1238, 1165, 1144, 1113, 1107, 1096, 1028, 1007 cm^{-1}. EIMS *m/z* (20 eV): 505 (M^+, 8), 448 (99), 419 (100), 199 (99), 151 (72). *Anal.* Found: C, 71.17; H, 7.52%. Calcd. for $C_{30}H_{36}O_5Si$: C, 71.39; H, 7.19%.

(1R,2R,3S)-2-(tert-Butyldiphenylsilyl)oxymethyl-1-(3,4-dimethoxyphenyl)-3-methyl-4-pivaloyloxy-1-butanol (**20**). To a solution of lactone **19** (0.39 g, 0.77 mmol) in toluene (8 ml) was added diisobutylaluminum hydride (0.90 ml, 1 M in toluene, 0.90 mmol) at −75°C. After the reaction solution had been stirred at −75°C for 30 min, a 6 M HCl soln. and EtOAc were added. The organic solution was separated, successively washed with a sat. aq. $NaHCO_3$ soln. and brine, and dried (Na_2SO_4). Concentration gave a crude hemiacetal. To an ice-cooled solution of this crude hemiacetal in EtOH (5 ml) was added sodium borohydride (55 mg, 1.45 mmol). The reaction mixture was stirred at room temperature for 1 h before adding EtOAc and a 1 M aq. HCl soln.. After next adding a sat. aq. $NaHCO_3$ soln., 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). Concentration gave a crude diol. To an ice-cooled solution of this crude diol in pyridine (2 ml) was added pivaloyl chloride (0.095 ml, 0.77 mmol). The reaction mixture was stirred in an ice bath for 1 h before adding H_2O and EtOAc. The organic solution was separated, successively washed with a 1 M aq. HCl soln., sat. aq. $NaHCO_3$ soln. and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave pivaloyl ester **20** (0.41 g, 0.69 mmol, 90%) as a colorless oil, $[\alpha]_D^{20} = -16$ (*c* 0.50, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.78 (3H, d, J = 6.8 Hz), 1.09 (9H, s), 1.18 (9H, s), 1.86 (1H, m), 2.13 (1H, m), 3.77 (1H, dd, J = 10.7, 4.9 Hz), 3.85 (1H, dd, J = 10.7, 3.4 Hz), 3.86 (3H, s), 3.89 (3H, s), 4.03 (1H, dd, J = 11.2, 5.4 Hz), 4.12 (1H, dd, J = 11.2, 5.1 Hz), 4.29 (1H, d, J = 5.9 Hz), 4.96 (1H, dd, J = 5.9, 5.4 Hz), 6.83 (1H, d, J = 8.3 Hz), 6.87 (1H, dd, J = 8.3, 2.0 Hz), 6.94 (1H, d, J = 2.0 Hz), 7.34–7.47 (6H, m), 7.56–7.58 (2H, m), 7.64–7.66 (2H, m). NMR δ_C ($CDCl_3$): 13.9, 19.0, 26.9, 27.2, 30.9, 38.8, 47.4, 55.7, 55.9, 63.1, 67.2, 75.4, 109.1, 111.0, 118.2, 127.8, 127.9, 130.0, 130.1, 132.2, 135.5, 135.7, 136.4, 148.1, 149.0, 178.2. IR ν_{max} ($CHCl_3$): 3490, 2967, 1721, 1516, 1464, 1429, 1285, 1262, 1237, 1161, 1142, 1113, 1064, 1030 cm^{-1}. EIMS m/z (20 eV): 593 ($M^+ + 1$, 28), 435 (93), 368 (80), 283 (100). *Anal.* Found: C, 70.64; H, 8.14%. Calcd. for $C_{35}H_{48}O_6Si$: C, 70.91; H, 8.16%.

(1R,2R,3S)-2-(tert-Butyldiphenylsilyl)oxymethyl-1-methoxymethoxy-1-(3,4-dimethoxyphenyl)-3-methyl-4-pivaloyloxybutane (**21**). To a solution of benzyl alcohol **20** (0.36 g, 0.61 mmol) and *N,N*-diisopropylethylamine (3.46 ml, 19.9 mmol) in CH_2Cl_2 (2 ml) was added chloromethyl methyl ether (0.72 ml, 9.48 mmol). After the reaction mixture had been stirred at room temperature for 15 h, MeOH, H_2O, and CH_2Cl_2 were successively added. The organic solution was separated, successively washed with a 1 M aq. HCl soln., $NaHCO_3$ soln., and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave methoxymethyl ether **21** (0.36 g, 0.57 mmol, 93%) as a colorless oil, $[\alpha]_D^{20} = +59$ (*c* 0.70, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.85 (3H, d, J = 6.8 Hz), 1.05 (9H, s), 1.17 (9H, s), 1.87 (1H, m), 2.22 (1H, m), 3.11 (3H, s), 3.81 (3H, s), 3.85 (1H, dd, J = 10.7, 2.4 Hz), 3.87 (3H, s), 3.94 (1H, dd, J = 10.7, 4.4 Hz), 4.06 (1H, dd, J = 10.7, 6.8 Hz), 4.12 (1H, dd, J = 10.7, 7.3 Hz), 4.36 (1H, d, J = 6.6 Hz), 4.39 (1H, d, J = 6.6 Hz), 4.56 (1H, d, J = 7.3 Hz), 6.74–6.79 (3H, m), 7.33–7.44 (6H, m), 7.62–7.64 (2H, m), 7.66–7.68 (2H, m). NMR δ_C ($CDCl_3$): 12.7, 19.1, 26.9, 27.2, 32.3, 38.7, 47.2, 55.8, 61.7, 68.5, 77.6, 94.2, 110.0, 110.7, 120.1, 127.6, 129.5, 129.6, 132.5, 133.5, 133.6, 135.6, 148.5, 149.0, 178.2. IR ν_{max} ($CHCl_3$): 2934, 1719, 1514, 1464, 1287, 1262, 1163, 1142, 1113, 1105, 1088, 1030 cm^{-1}. EIMS m/z (20 eV): 637 ($M^+ + 1$, 23), 319 (91), 247 (100). *Anal.* Found: C, 69.76; H, 8.52%. Calcd. for $C_{37}H_{52}O_7Si$: C, 69.78; H, 8.23%.

(2S,3R,4R)-3-(tert-Butyldiphenylsilyl)oxymethyl-4-methoxymethoxy-4-(3,4-dimethoxyphenyl)-2-methyl-1-butanol (**22**). To a solution of pivaloyl ester **21** (0.34 g, 0.53 mmol) in toluene (5 ml) was added diisobutylaluminum hydride (1.17 ml, 1 M in toluene, 1.17 mmol) at −75°C. After the reaction solution had been stirred at −75°C for 30 min, a 6 M aq. HCl soln. and then EtOAc were added. The organic solution was separated, successively washed with a sat. aq. $NaHCO_3$ soln. and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/2) gave alcohol **22** (0.27 g, 0.49 mmol, 92%) as a colorless oil, $[\alpha]_D^{20} = +88$ (*c* 0.40, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.82 (3H, d, J = 7.3 Hz), 1.08 (9H, s), 1.58–1.69 (2H, m), 2.29 (1H, m), 2.99 (3H, s), 3.52–3.62 (2H, m), 3.80 (1H, dd, J = 10.7, 10.3 Hz), 3.83 (3H, s), 3.87 (3H, s), 4.02 (1H, dd, J = 10.7, 3.4 Hz), 4.26 (1H, d, J = 6.8 Hz), 4.33 (1H, d, J = 6.8 Hz), 4.34 (1H, d, J = 8.3 Hz), 6.76–6.77 (3H, m), 7.35–7.46 (6H, m), 7.67–7.71 (4H, m). NMR δ_C ($CDCl_3$): 11.6, 19.1, 26.8, 34.8, 48.8, 55.7, 55.8, 55.9, 61.7, 67.6, 77.7, 93.9, 110.2, 110.7, 120.4, 127.7, 129.7, 129.8, 132.1, 132.8, 133.0, 135.6, 135.7, 148.6, 149.1. IR ν_{max} ($CHCl_3$): 3375, 2934, 1516, 1466, 1262, 1157, 1140, 1113, 1107, 1030 cm^{-1}. EIMS m/z (20 eV): 552 (M^+, 8), 434 (98), 405 (90), 283 (64), 213 (100). HRMS (EI) m/z (M^+): Calcd. for $C_{32}H_{44}O_6Si$, 552.2903; found, 552.2869.

(2S,3R,4R)-3-(tert-Butyldiphenylsilyl)oxymethyl-4-methoxymethoxy-4-(3,4-dimethoxyphenyl)-2-methylbutanal (**23**). A reaction mixture of alcohol **22** (0.27 g, 0.49 mmol), pyridinium chlorochromate (0.13 g, 0.60 mmol) and 4A molecular sieves (0.2 g) in CH_2Cl_2 (10 ml) was stirred at room temperature

for 1 h before adding ether. After the mixture had been filtered, the filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc/hexane = 1/2) to give aldehyde **23** (0.24 g, 0.44 mmol, 90%) as a colorless oil, $[\alpha]_D^{20} = +75$ (*c* 0.20, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.03 (9H, s), 1.06 (3H, d, *J* = 6.8 Hz), 2.01 (1H, m), 2.82 (1H, m), 3.02 (3H, s), 3.62 (1H, dd, *J* = 10.3, 10.3 Hz), 3.86 (3H, s), 3.87 (3H, s), 4.01 (1H, dd, *J* = 10.3, 4.9 Hz), 4.26 (1H, d, *J* = 6.8 Hz), 4.34 (1H, d, *J* = 6.8 Hz), 4.40 (1H, d, *J* = 8.8 Hz), 6.80–6.81 (3H, m), 7.36–7.45 (6H, m), 7.63–7.65 (4H, m), 9.68 (1H, s). NMR δ_C ($CDCl_3$): 8.1, 19.1, 26.7, 45.2, 48.0, 55.7, 55.9, 62.3, 93.8, 109.9, 110.8, 120.5, 127.7, 129.7, 131.5, 133.1, 133.2, 135.6, 135.7, 149.0, 149.3, 203.7. IR ν_{max} ($CHCl_3$): 2934, 1725, 1516, 1464, 1428, 1262, 1238, 1142, 1113, 1105, 1078, 1028 cm^{-1}. EIMS *m/z* (20 eV): 551 ($M^+ + 1$, 25), 433 (100), 244 (55). *Anal.* Found: C, 69.59; H, 7.73%. Calcd. for $C_{32}H_{42}O_6Si$: C, 69.78; H, 7.69%.

(1RS,2S,3R,4R)-3-(tert-Butyldiphenylsilyl) oxymethyl-4-methoxymethoxy-4-(3,4-dimethoxyphenyl)-2-methyl-1-(3,4-methylenedioxyphenyl)-1-butanol (**24**). After a mixture of Mg (0.20 g, 8.23 mg atom) and 4-bromo-1,2-methylenedioxybenzene (0.10 ml, 0.83 mmol) in THF (3 ml) had been heated under refluxing for 30 min, aldehyde **23** (0.10 g, 0.18 mmol) in THF (2 ml) was added at 0°C. The reaction mixture was stirred at 0°C for 1 h before adding a sat. aq. NH_4Cl soln. and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/4) gave benzyl alcohol **24** (0.11 g, 0.16 mmol, 89%) as a mixture of 1*R*/*S* isomers. NMR δ_H ($CDCl_3$): 0.86 (1.5H, d, *J* = 7.3 Hz), 0.99 (1.5H, d, *J* = 7.3 Hz), 1.11 (4.5H, s), 1.13 (4.5H, s), 1.63 (1H, br. s), 1.76 (0.5H, m), 1.87 (0.5H, m), 2.24 (0.5H, m), 2.39 (0.5H, m), 2.92 (1.5H, s), 2.97 (1.5H, s), 3.68–3.89 (1H, m), 3.74 (1.5H, s), 3.79 (1.5H, s), 3.86 (1.5H, s), 3.88 (1.5H, s), 4.05 (0.5H, dd, *J* = 10.3, 3.9 Hz), 4.06 (0.5H, dd, *J* = 10.3, 3.9 Hz), 4.12 (0.5H, d, = 8.8 Hz), 4.16 (0.5H, d, *J* = 6.8 Hz), 4.23 (1H, d, *J* = 6.8 Hz), 4.30 (0.5H, d, *J* = 6.8 Hz), 4.31 (0.5H, d, *J* = 8.8 Hz), 4.52 (0.5H, br. s), 4.72 (0.5H, d, *J* = 3.9 Hz), 5.90–5.94 (2H, m), 6.45 (0.5H, s), 6.54–6.58 (1.5H, m), 6.61–6.73 (3.5H, m), 6.76 (0.5H, d, *J* = 7.8 Hz), 7.37–7.46 (6H, m), 7.65–7.74 (4H, m). NMR δ_C ($CDCl_3$): 8.2, 12.8, 19.1, 26.8, 26.9, 40.3, 40.8, 44.6, 50.0, 55.6, 55.8, 55.9, 62.2, 62.5, 78.4, 78.7, 93.7, 93.9, 100.7, 100.8, 106.7, 106.9, 107.5, 107.6, 109.6, 109.8, 110.2, 110.6, 119.3, 119.5, 120.5, 127.7, 127.8, 129.8, 129.9, 131.8, 132.2, 132.4, 132.7, 132.8, 135.4, 135.7, 138.1, 138.5, 146.1, 147.3, 148.6, 148.7, 149.0, 149.1. IR ν_{max} ($CHCl_3$): 3376, 2936, 1516, 1505, 1489, 1466, 1443, 1429, 1260, 1238, 1159, 1152, 1140, 1113, 1105, 1042, 1028 cm^{-1}. EIMS *m/z* (20 eV): 673 ($M^+ + 1$, 8), 553 (99), 460 (80), 425 (100), 338 (93), 211 (52), 166 (61). *Anal.* Found: C, 67.95; H, 7.25%. Calcd. for $C_{39}H_{48}O_8Si \cdot H_2O$: C, 67.80; H, 7.29%.

(1RS,2S,3R)-3-[(1R)-1-Methoxymethoxy-1-(3,4-dimethoxyphenyl)methyl]-2-methyl-1-(3,4-methylenedioxyphenyl)-1,4-butanediol (**25**). To an ice-cooled solution of silyl ether **24** (0.11 g, 0.16 mmol) in THF (10 ml) was added tetrabutylammonium fluoride (0.20 ml, 1 M in THF, 0.20 mmol). After the reaction solution had been stirred at 0°C for 1 h, a sat. aq. NH_4Cl soln. and EtOAc were successively added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 2/1 and 4/1) gave diol **25** (60 mg, 0.14 mmol, 88%) as a mixture of 1*R*/*S* isomers. NMR δ_H ($CDCl_3$): 0.88 (1.5H, d, *J* = 7.3 Hz), 0.94 (1.5H, d, *J* = 7.3 Hz), 1.56 (0.5H, m), 1.63 (0.5H, m), 1.91 (0.5H, m), 2.35 (0.5H, m), 2.34 (1.5H, s), 3.36 (1.5H, s), 3.78 (1.5H, s), 3.79 (1.5H, s), 3.80–3.92 (1.5H, m), 3.89 (3H, s), 3.99 (0.5H, dd, *J* = 11.2, 5.4 Hz), 4.35–4.52 (3.5H, m), 4.55 (0.5H, d, *J* = 9.8Hz), 5.91–5.94 (2H, m), 6.46–6.47 (1H, m), 6.53–6.60 (2H, m), 6.66–6.70 (2H, m), 6.72–6.80 (1H, m). NMR δ_C ($CDCl_3$): 9.6, 12.3, 39.3, 39.4, 44.7, 48.4, 55.6, 55.7, 55.8, 55.9, 61.2, 62.2, 77.4, 80.3, 81.1, 93.6, 100.9, 101.0, 106.5, 106.6, 107.6, 107.7, 109.5, 109.7, 110.2, 110.4, 119.3, 120.0, 121.0, 121.1, 131.6, 131.7, 137.5, 137.7, 146.4, 146.8, 147.5, 147.6, 148.8, 149.0, 149.2, 149.3. IR ν_{max} ($CHCl_3$): 3611, 2894, 1518, 1505, 1489, 1466, 1443, 1260, 1238, 1142, 1040, 1028, 920, 911 cm^{-1}. EIMS *m/z* (20 eV): 434 (M^+, 4), 222 (100), 191 (94), 151 (99). HRMS (EI) *m/z* (M^+): Calcd. for $C_{23}H_{30}O_8$, 434.1938; found, 434.1942.

(2S,3R)-3-[(1R)-1-Methoxymethoxy-1-(3,4-dimethoxyphenyl)methyl]-2-methyl-4-butanolide (**26**). To a mixture of benzyl alcohol lactone **18** (0.16 g, 0.60 mmol) and *N*,*N*-diisopropylethylamine (0.86 ml, 4.94 mmol) in CH_2Cl_2 (1 ml) was added chloromethyl methyl ether (0.18 ml, 2.37 mmol). The reaction mixture was stirred at room temperature for 48 h before the successive addition of MeOH, H_2O and CH_2Cl_2. The organic solution was separated, successively washed with a 1 M aq. HCl soln., sat. aq. $NaHCO_3$ soln. and brine, and dried (Na_2SO_4). Concentrated followed by silica gel column chromatography (EtOAc/hexane = 1/1) gave methoxymethyl ether **26** (0.16 g, 0.52 mmol, 87%) as a colorless oil, $[\alpha]_D^{20} = +147$ (*c* 0.40, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.29 (3H, d, *J* = 7.3 Hz), 2.35 (1H, m), 2.87 (1H, m), 3.37 (3H, s), 3.89 (6H, s), 4.32 (1H, dd, *J* = 9.8, 7.1 Hz), 4.39 (1H, dd, *J* = 9.8, 5.4 Hz), 4.47 (1H, d, *J* = 6.8 Hz), 4.49 (1H, d, *J* = 6.8 Hz), 4.74 (1H, d, *J* = 6.3 Hz), 6.82 (1H, s), 6.87 (2H, s). NMR δ_C

($CDCl_3$): 9.8, 36.5, 45.2, 55.9, 56.0, 56.4, 68.0, 75.6, 77.2, 94.0, 109.8, 111.1, 119.8, 131.1, 149.1, 149.4, 179.5. IR ν_{max} ($CHCl_3$): 2938, 1773, 1518, 1464, 1262, 1237, 1181, 1159, 1140, 1028 cm^{-1}. EIMS *m/z* (20 eV): 310 (M^+, 40), 211 (87), 151 (100). HRMS (EI) *m/z* (M^+): calcd. for $C_{16}H_{22}O_6$, 310.1415; found, 310.1405.

Conversion of 26 to diol 25. To a solution of lactone **26** (0.14 g, 0.45 mmol) was added diisobutylaluminum hydride (0.54 ml, 1 M in toluene, 0.54 mmol) at −75°C. After stirring at −75°C for 30 min, a 6 M aq. HCl soln. and EtOAc were added. The organic solution was separated, successively washed with sat. aq. $NaHCO_3$ soln. and brine, and dried (Na_2SO_4). Concentration gave a crude hemiacetal. A mixture of Mg (0.50 g, 21 mg atom) and 4-bromo-1,2-methylenedioxybenzene (0.25 ml, 2.08 mmol) in THF (4 ml) was heated under refluxing for 30 min before adding the crude hemiacetal in THF (1 m). The resulting reaction mixture was heated under refluxing for 20 h. After adding a sat. aq. NH_4Cl soln. and EtOAc, the organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 2/1) gave diol **25** (0.17 g, 0.39 mmol, 87%) as a mixture of 1*R*/*S* isomers.

(2S,3S,4R)-4-[(1R)-1-Methoxymethoxy-1-(3,4-dimethoxyphenyl)methyl]-3-methyl-2-(3,4-methylenedioxyphenyl)tetrahydrofuran (**27**). A reaction solution of diol **25** (20 mg, 0.046 mmol) and 10-camphorsulfonic acid (2 mg, 0.0086 mmol) in CH_2Cl_2 (4 ml) was stirred at 0°C for 16 h before adding a few drops of triethylamine. After concentration, the residue was applied to silica gel column chromatography (EtOAc/hexane = 1/1) to give protected (+)-magnostellin C **27** (12 mg, 0.029 mmol, 63 %) as a colorless oil, $[\alpha]_D^{20} = +166$ (*c* 0.50, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.04 (3H, d, *J* = 6.8 Hz), 1.90 (1H, m), 2.80 (1H, m), 3.37 (3H, s), 3.84 (3H, s), 3.87 (3H, s), 4.05 (1H, dd, *J* = 8.8, 8.8 Hz), 4.39 (1H, dd, *J* = 8.8, 7.8 Hz), 4.39 (1H, d, *J* = 6.8 Hz), 4.46 (1H, d, *J* = 6.8 Hz), 4.59 (1H, d, *J* = 6.8 Hz), 4.61 (1H, br. s), 5.93 (2H, s), 6.71–6.75 (2H, m), 6.79–6.82 (3H, m), 6.86–6.88 (1H, m). NMR δ_C ($CDCl_3$): 13.9, 43.1, 47.1, 55.8, 55.9, 70.7, 77.2, 88.1, 93.3, 100.9, 106.0, 107.9, 110.5, 110.8, 118.6, 120.6, 132.2, 137.3, 146.6, 147.6, 148.8, 149.1. IR ν_{max} ($CHCl_3$): 2938, 1518, 1507, 1489, 1466, 1443, 1260, 1238, 1142, 1096, 1040, 1028 cm^{-1}. EIMS *m/z* (20 eV): 416 (M^+, 36), 354 (99), 211 (100), 177 (99), 151 (99). HRMS (EI) *m/z* (M^+): calcd. for $C_{23}H_{28}O_7$, 416.1834; found, 416.1858.

(2S,3S,4R)-4-[(1R)-1-Hydroxy-1-(3,4-dimethoxyphenyl)methyl]-3-methyl-2-(3,4-methylenedioxyphenyl)tetrahydrofuran [(+)-magnostellin C] (**1**). To an ice-cooled solution of methoxymethyl ether **27** (16 mg, 0.038 mmol) in CH_2Cl_2 (8 ml) was added bromotrimethylsilane (10 µl, 0.076 mmol). The reaction solution was stirred at 0°C for 30 min, and then a sat. aq. $NaHCO_3$ soln. and CH_2Cl_2 were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel TLC (EtOAc/hexane = 1/1) gave (+)-magnostellin C (**1**; 8 mg, 0.021 mmol, 55%) as a colorless oil, $[\alpha]_D^{20} = +97$ (*c* 0.30, $CHCl_3$), lit.[1] $[\alpha]_D^{20} = +56.3$ (*c* 1.67, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.11 (3H, d, *J* = 7.3 Hz), 1.87 (1H, br. s), 2.08 (1H, m), 2.70 (1H, m), 3.88 (6H, s), 4.10 (1H, dd, *J* = 8.8, 6.8 Hz), 4.22 (1H, dd, *J* = 8.8, 7.6 Hz), 4.58 (1H, d, *J* = 6.4 Hz), 4.84 (1H, br. s, by D_2O exchange d, *J* = 6.4 Hz), 5.94 (2H, s), 6.76–6.78 (2H, m), 6.82–6.85 (3H, m), 6.89–6.90 (1H, m). NMR δ_C ($CDCl_3$): 13.0, 44.2, 48.1, 55.9, 69.5, 73.1, 87.9, 100.9, 106.2, 108.0, 109.4, 111.1, 118.3, 119.1, 136.2, 137.0, 146.7, 147.7, 148.6, 149.1 cm^{-1}. IR ν_{max} ($CHCl_3$): 3604, 3021, 2963, 1516, 1507, 1489, 1464, 1443, 1252, 1240, 1140, 1042, 1028 cm^{-1}. EIMS *m/z* (20 eV): 372 (M^+, 44), 177 (96), 167 (100). HRMS (EI) *m/z* (M^+): calcd. for $C_{21}H_{24}O_6$, 372.1571; found, 372.1589.

Acknowledgments

We measured the 400 MHz NMR data at Advanced Instrumentation Center For Chemical Analysis Ehime University. We thank the staff of this center for EIMS measurements.

References

1) Kato, M. J., Fo, H. F. P., Yoshida, M., and Gottlieb, O. R., Neolignans from fruits of *Virola elongata*. *Phytochemistry*, **25**, 279–280 (1986).
2) a) MacRae, W. D., and Towers, G. H. N., Biological activities of lignans. *Phytochemistry*, **23**, 1207–1220 (1984); b) Ayres, D. C., and Loike, J. D., Lignans. Cambridge University Press, Cambridge (1990).
3) Yamauchi, S., and Kinoshita, Y., Stereoselective model synthesis of the optically active olivil type of lignan from D-xylose. *Biosci. Biotechnol. Biochem.*, **64**, 1563–1571 (2000).
4) Yamauchi, S., and Kinoshita, Y., Synthesis of optically active olivil type of lignan from L-arabinose using *threo*-selective aldol condensation as a key reaction. *Biosci. Biotechnol. Biochem.*, **64**, 2320–2327 (2000).
5) Hanessian, S., Delorme, D., and Dufresne, Y., Mild Cleavage of methoxymethyl (MOM) ethers with trimethylsilyl bromide. *Tetrahedron Letters*, **25**, 2515–2518 (1984).