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Synthesis of (+)-Aptosimon, a 4-Oxofurofuran Lignan, by *erythro* Selective Aldol Condensation and Stereoconvergent Cyclization as the Key Reactions

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The 4-oxofurofuran lignan, (+)-aptosimon (1), was synthesized from γ-butyrolactone (9). To construct the two benzylic chiral center of (+)-aptosimon (1), highly *erythro* selective aldol condensation and stereoconvergent SN1 intramolecular cyclization were used as the key reactions.

Key words: lignan; furofuran lignan; aptosimon; aldol condensation

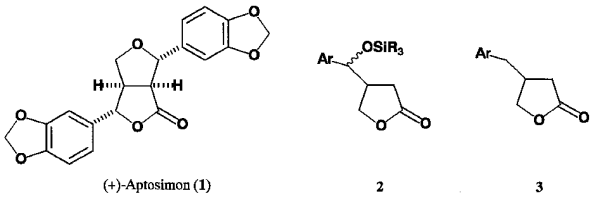

Fig.

(+)-Aptosimon has been isolated from *Aptosimum spinescens*[1] and its structure corrected to that of **1**.[2] Since 4-oxofurofuran lignan is a small group in the furofuran series,[3] only five synthetic studies on the racemate have been reported.[4–8] Though many types of biological activity for furofuran lignan have been reported,[9,10] *e.g.* antioxidative activity, antitumor activity, phosphodiesterase inhibition activity, and the effect on the central nervous system, the structure-activity relationship is unknown. To contribute to this biological research, and particularly to study the relationship between activity and degree of oxygenation of the furofuran structure, 1,2-oxygenated furofuran lignan has been synthesized.[11] As a continuation of this research, the 4-oxofurofuran lignan, (+)-aptosimon (**1**), has been selected as the target compound in this work.

In this synthetic study, *erythro* or *threo* selectivity in the aldol condensation of β-[(aryl)(silyloxy) methyl]-γ-butyrolactone **2** with piperonal *via* potassium enolate is also interesting. In our previous study, aldol condensation using the potassium enolate of β-benzyl-γ-butyrolactone **3** and benzaldehydes showed *erythro* selectivity.[12] As a new substrate for this aldol condensation, oxygenated β-benzyl-γ-butyrolactone **2** is employed. The *erythro* selectivity in this aldol condensation with **2** is very important in this project (Fig.).

The retrosynthetic analysis of (+)-aptosimon (**1**) is shown in Scheme 1. (+)-Aptosimon (**1**) could be obtained by the cyclization of **4** followed by oxidation. Tetrahydrofuran derivative **4** could be obtained from triol **5** by employing stereoconvergent SN 1 cyclization between oxygen at the 4 position and 1′-benzylic position of **5** in the presence of a catalytic amount of acid. *Erythro* aldol product **6** could be converted to triol **5** by protection, reduction, and selective removal of R_1. The high *erythro* selectivity in the aldol condensation between γ-butyrolactone **7** and piperonal would be required to give **6**. Aldol product **8** could be converted to γ-butyrolactone **7**. This aldol product **8** would be obtained from γ-butyrolactone **9** and piperonal; however, the *erythro* or *threo* selectivity would not be necessary in this step. γ-Butyrolactone **9** can be obtained from L-glutamic acid.[13] The chiral center at the 2 position of (+)-aptosimon (**1**) could be converted from the 2′ position of **6**, which could be obtained by *erythro* selective aldol condensation, and the other chiral center at the 6 position could be obtained by the stereoconvergent cyclization of triol **5**.

Results and Discussion

The enantiomeric excess of the starting material was determined before tritylation to **9** as 99% ee by Mosher's method. The aldol condensation of γ-butyrolactone **9**[13] with piperonal, using lithium diisopropylamide, gave *erythro* aldol product **10** (43%) and *threo* aldol product **11** (43%). Although the *erythro* or *threo* selectivity at this stage was not important, the next step was performed from separated *erythro* aldol product **10** and *threo* aldol product **11**. The *erythro* and *threo* isomers were determined by the coupling constant between 2-H and the benzylic proton.[14]

After the hydroxy group of *erythro* **10** had been protected as a triisopropylsilyl ether (85%), resulting

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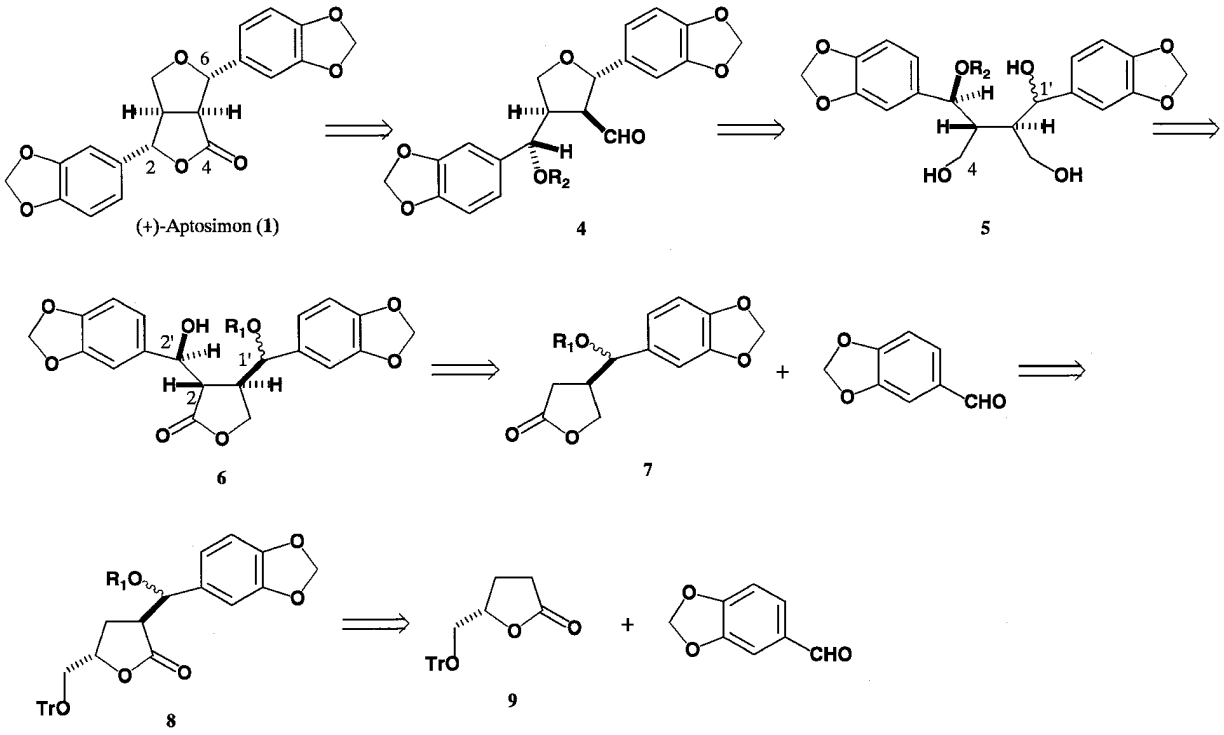


Scheme 1. Retrosynthetic Analysis of (+)-Aptosimon (**1**).

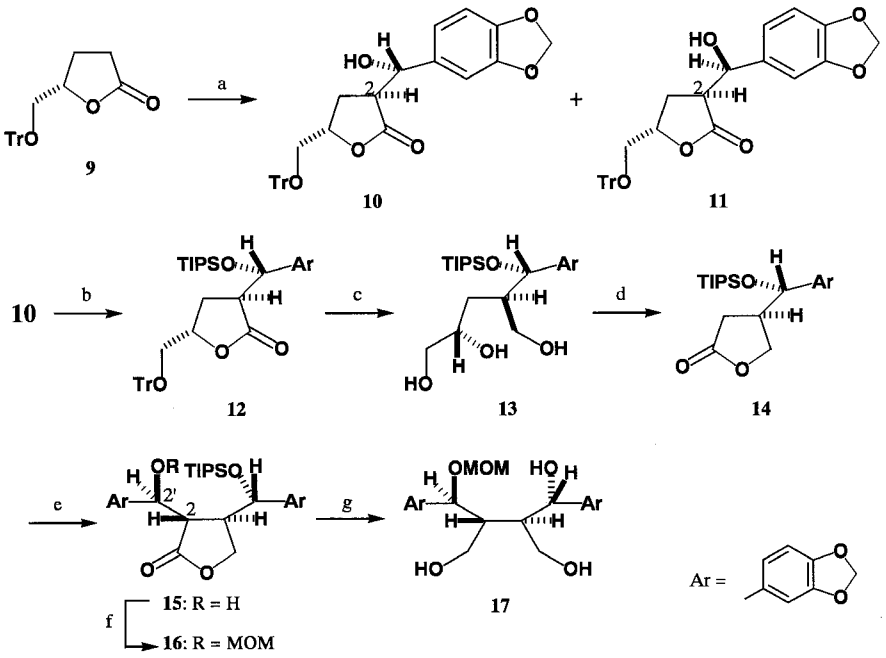
lactone **12** was subjected to $LiAlH_4$ reduction and subsequent cleavage of the trityl ether in formic acid-ether to give triol **13** in 69% yield in 2 steps. $NaIO_4$ followed by Ag_2CO_3-celite oxidation of triol **13** gave γ-butyrolactone **14** in 71% yield in 2 steps. This lactone **14** was exposed to the important aldol condensation requiring *erythro* selectivity. This *erythro* selectivity was achieved by using potassium bis(trimethylsilyl)amide as a base, giving *erythro* aldol product **15** as a single isomer in 84% yield. This *erythro* configuration was confirmed by the coupling constant between 2-H and benzylic 2′-H.[14] After the hydroxy group had been protected as a methoxymethyl ether in a quantitative yield, lactone **16** was transformed to triol **17** by $LiAlH_4$ reduction and then by cleavage of the silyl ether with $(n\text{-Bu})_4NF$ in 75% yield in 2 steps (Scheme 2).

Threo aldol product **11** was converted to lactone **20** in 54% overall yield by the same method as that described for the preparation of lactone **14**. Aldol condensation of the potassium enolate of lactone **20** with piperonal also gave *erythro* aldol product **21** as a single isomer in 86% yield. These results show that the presence of a silyloxy group at the benzylic position of β-benzyl-γ-butyrolactone did not reduce the *erythro* selectivity and that the stereochemistry at this benzylic position did not effect the *erythro* selectivity in the aldol condensation *via* potassium enolate.

After protecting the hydroxy group as a methoxymethyl ether in 82% yield, resulting lactone **22** was treated with diisobutylaluminum hydride and $NaBH_4$ and then by $(n\text{-Bu})_4NF$ to give triol **23** in a quantitative yield in 3 steps. The treatment of **22** with $LiAlH_4$ gave a desilylated product (scheme 3).

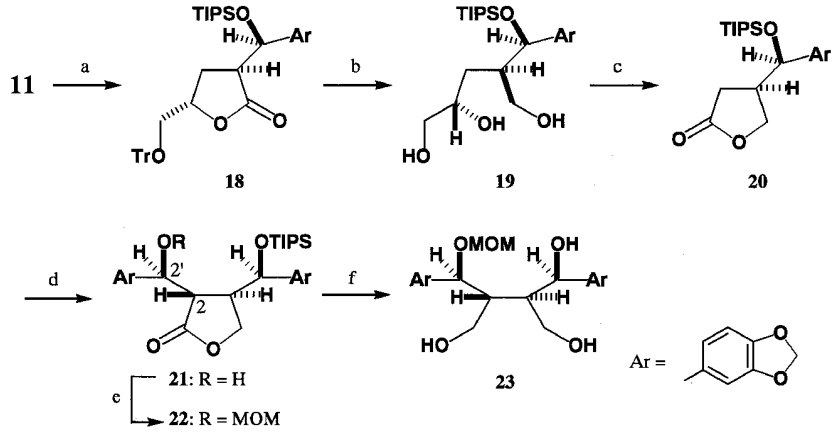
SN1 intramolecular etherification of triols **17** and **23** was carried out by employing 10-camphorsulfonic acid as a catalyst, giving stereoconvergently tetrahydrofuran derivative **24** as a single isomer in 61% and 57% yield, respectively. The conversion of **17** to **24** proceeded smoothly, although that of **23** took a long time. At this stage, the construction of two benzylic chiral centers of (+)-aptosimon (**1**) was accomplished. After pyridinium chlorochromate oxidation of **24** to aldehyde **25** in 73% yield, subsequent cleavage of the methoxymethyl ether in a 6 M aqueous HCl solution and tetrahydrofuran gave hemiacetal **26** in 82% yield. Finally, hemiacetal **26** was subjected to pyridinium chlorochromate oxidation to give (+)-aptosimon (**1**) in 84% yield. The existence of NOE between the two benzylic protons and 8β-H supports this absolute configuration (Scheme 4).

(+)-Aptosimon (**1**) was thus synthesized from γ-butyrolactone **9**, involving 14–15 steps in 6–10% overall yield. This is the first synthesis of optically active 4-oxofurofuran lignan, and highly *erythro* selective aldol condensation of β-[(aryl)(silyloxy) methyl]-γ-butyrolactone with piperonal, using KHMDS, was observed. The two benzylic chiral centers of (+)-aptosimon (**1**) were constructed by this *erythro* selective aldol condensation and stereoconvergent SN1 intramolecular cyclization.



Scheme 2. Conversion to Triol **17**.

(a) LDA, piperonal, THF, −75°C, 1 h (**10**, 43% yield; **11**, 43% yield). (b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 1 h (85% yield). (c) (1) $LiAlH_4$, THF, 0°C, 1 h; (2) HCO_2H, ether, −10°C, 10 min (69% yield, 2 steps). (d) (1) $NaIO_4$, MeOH, r.t., 2 h; (2) Ag_2CO_3-celite, toluene, reflux, 1 h (71% yield, 2 steps). (e) KHMDS, piperonal, THF, −75°C, 1 h (84% yield). (f) MOMCl, DIPEA, CH_2Cl_2, r.t., 16 h (100% yield). (g) (1) $LiAlH_4$, THF, r.t., 30 min; (2) $(n\text{-Bu})_4NF$, THF, 0°C, 1 h (75% yield, 2 steps).



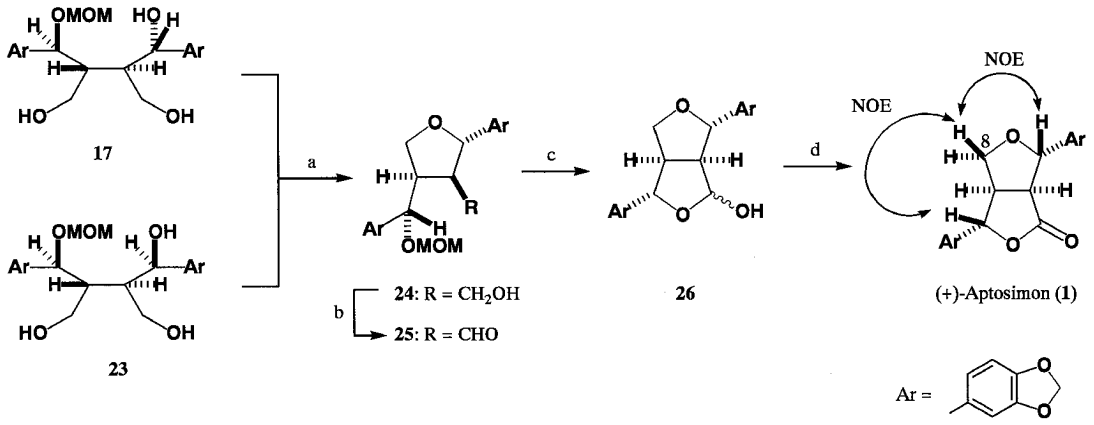
Scheme 3. Conversion to Triol **23**.

(a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 1 h (90% yield). (b) (1) $LiAlH_4$, THF, 0°C, 1 h; (2) HCO_2H, ether, −10°C, 10 min (61% yield, 2 steps). (c) (1) $NaIO_4$, MeOH, r.t., 2 h; (2) Ag_2CO_3-celite, toluene, reflux, 1 h (99% yield, 2 steps). (d) KHMDS, piperonal, THF, −75°C, 1 h (86% yield). (e) MOMCl, DIPEA, CH_2Cl_2, r.t., 16 h (82% yield). (f) (1) DIBAL-H, −75°C, 1 h; (2) $NaBH_4$, EtOH, r.t., 2 h; (3) $(n\text{-Bu})_4NF$, THF, 0°C, 1 h (100% yield, 3 steps).

Experimental

All melting point (mp) data are uncorrected. NMR data were measured by a JNM-EX400 spectrometer, IR spectra were determined with a Shimadzu FTIR-8100 spectrophotometer, FABMS data were measured with a JMS-MS700V 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).

*(2S,4S)-2-[(S)-(Hydroxy)(3,4-methylenedioxyphenyl)methyl]-5-trityloxy-4-pentanolide (**10**)* and *(2S,4S)-2-[(R)-(hydroxy)(3,4-methylenedioxyphenyl)methyl]-5-trityloxy-4-pentanolide (**11**)*. To a solution of LDA (0.067 mol) in THF (200 ml) was added a solution of lactone **9** (20.0 g, 0.056 mol) in THF (60 ml) at −75°C. After the solution was



Scheme 4. Conversion to (+)-Aptosimon (**1**).
(a) for **17**: CSA, CH_2Cl_2, 3°C, 4 h (61% yield); for **23**: CSA, CH_2Cl_2, 3°C, 40 h (57% yield). (b) PCC, MS 4A, CH_2Cl_2, r.t., 7 h (73% yield). (c) aq. 6 M HCl solution, THF, r.t., 5 h (82% yield). (d) PCC, MS 4A, CH_2Cl_2, r.t., 3 h (84% yield).

stirred at −75°C for 30 min, a solution of piperonal (12.6 g, 0.084 mol) in THF (40 ml) was added. The reaction solution was stirred at −75°C for 1 h, and then a sat. aq. NH_4Cl solution was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (2% EtOAc/benzene) gave *erythro* **10** (12.2 g, 0.024 mol, 43%) as colorless crystals, mp 135–136°C (*iso*-Pr2O/benzene = 1/1) and *threo* **11** (12.2 g, 0.024 mol, 43%) as colorless crystals, mp 158–159°C (*iso*-Pr_2O/benzene = 1/1). *Erythro* **10**: $[\alpha]_D^{20} = +1.1$ (*c* 0.94, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.80 (1H, ddd, *J* = 12.9, 9.8, 3.4 Hz, 3-*H*H), 2.40 (1H, ddd, *J* = 12.9, 9.3, 8.8 Hz, 3-*H*H), 2.63 (1H, d, *J* = 3.9 Hz, OH), 3.08 (1H, dd, *J* = 10.7, 3.9 Hz, 5-*H*H), 3.16 (1H, ddd, *J* = 9.8, 9.3, 2.9 Hz, 2-H), 3.41 (1H, dd, *J* = 10.7, 3.2 Hz, 5-H*H*), 4.64 (1H, m, 4-H), 5.29 (1H, dd, *J* = 3.9, 2.9 Hz, Ar-C*H*OH), 5.95 (2H, s, OCH_2O), 6.77–6.80 (2H, m, ArH), 6.82–6.84 (1H, m, ArH), 7.20–7.30 (9H, m, ArH), 7.35–7.38 (6H, m, ArH). NMR δ_C ($CDCl_3$): 23.7, 48.1, 65.3, 71.1, 77.9, 87.0, 101.1, 106.0, 108.2, 118.6, 127.2, 127.9, 128.6, 135.7, 143.3, 147.0, 147.9, 178.1. IR ν_{max} ($CHCl_3$): 3500, 3011, 2961, 1763, 1505, 1491, 1449, 1240, 1184, 1096, 1080, 1042 cm^{-1}. *Anal.* Found: C, 75.35; H, 5.59%. Calcd. for $C_{32}H_{28}O_6$: C, 75.58; H, 5.55%. *Threo* **11**: $[\alpha]_D^{20} = +35.4$ (*c* 0.74, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.80 (1H, ddd, *J* = 13.0, 9.3, 2.4 Hz, 3-*H*H), 1.93 (1H, ddd, *J* = 13.0, 10.3, 9.3 Hz, 3-H*H*), 3.09 (1H, dd, *J* = 10.7, 3.9 Hz, C*H*HOTr), 3.17 (1H, m, 2-H), 3.43 (1H, dd, *J* = 10.7, 3.4 Hz, CH*H*OTr), 4.32 (1H, s, OH), 4.50 (1H, m, 4-H), 4.66 (1H, d, *J* = 8.8 Hz, ArC*H*OH), 5.96 (1H, d, *J* = 6.6 Hz, OCH*H*O), 5.96 (1H, d, J = 6.6 Hz, OCH*H*O), 6.77–6.78 (2H, m, ArH), 6.88 (1H, s, ArH), 7.22–7.32 (9H, m, ArH), 7.36–7.38 (6H, m, ArH). NMR δ_C ($CDCl_3$): 27.5, 46.3, 65.0, 74.9, 77.5, 87.3, 101.1, 106.8, 108.1, 120.4, 127.2, 127.3, 127.9, 128.0, 128.6, 128.7, 134.4, 143.2, 147.6, 148.0, 179.4. IR ν_{max} ($CHCl_3$): 3503, 3017, 2878, 1754, 1505, 1489, 1449, 1250, 1183, 1098, 1042 cm^{-1}. *Anal.* Found: C, 75.55; H, 5.55%. Calcd. for $C_{32}H_{28}O_6$: C, 75.58; H, 5.55%.

(2S,4S)-2-[(S)-(3,4-Methylenedioxyphenyl)(triisopropylsilyloxy)methyl]-5-trityloxy-4-pentanolide (12). To an ice-cooled solution of *erythro***10** (13.0 g, 0.026 mol) and 2,6-lutidine (6.56 ml, 0.057 mol) in CH_2Cl_2 (100 ml) was added TIPSOTf (7.69 ml, 0.029 mol). The reaction solution was stirred at 0°C for 1 h before addition of a sat. aq. $NaHCO_3$ solution. The organic solution was separated, washed with a sat. aq. $CuSO_4$ solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/19) gave silyl ether **12** (14.6 g, 0.022 mol, 85%) as colorless crystals, mp 108–109°C. $[\alpha]_D^{20} = -6.0$ (*c* 1.66, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.99–1.08 (21H, m, *iso*-Pr), 1.80 (1H, ddd, *J* = 12.7, 9.8, 3.4 Hz, 3-*H*H), 2.65 (1H, ddd, *J* = 12.7, 8.8, 8.8 Hz, 3-H*H*), 2.92 (1H, ddd, *J* = 9.8, 8.8, 2.0 Hz, 2-H), 3.07 (1H, dd, *J* = 10.5, 4.2 Hz, 5-*H*H), 3.39 (1H, dd, *J* = 10.5, 3.2 Hz, 5-*H*H), 4.65 (1H, m, 4-H), 5.44 (1H, d, *J* = 2.0 Hz, Ar-CHOTIPS), 5.96 (2H, s, OCH_2O), 6.75–6.79 (2H, m, ArH), 6.81–6.83 (1H, m, ArH), 7.19–7.28 (9H, m, ArH), 7.34–7.40 (6H, m, ArH). NMR δ_C ($CDCl_3$): 12.6, 17.9, 18.0, 23.0, 50.0, 65.5, 72.8, 77.7, 87.0, 101.0, 106.2, 108.1, 118.8, 127.1, 127.9, 128.6, 137.7, 143.4, 146.8, 147.6, 177.7. IR ν_{max} ($CHCl_3$): 3063, 2946, 2869, 1771, 1505, 1489, 1443, 1252, 1238, 1186, 1130, 1102, 1088, 1042, 1013, 980 cm^{-1}. *Anal.* Found: C, 74.17; H, 7.58%. Calcd. for $C_{41}H_{48}O_6Si$: C, 74.06; H, 7.28%.

(2S,4R)-4-[(S)-(3,4-Methylenedioxyphenyl)(triisopropylsilyloxy)methyl]pentane-1,2,5-triol (13). To an ice-cooled suspension of $LiAlH_4$ (0.98 g,

0.026 mol) in THF (20 ml) was added a solution of lactone *12* (17.3 g, 0.026 mol) in THF (80 ml). The reaction mixture was stirred at 0°C for 1 h before additions of a sat. aq. $MgSO_4$ solution and K_2CO_3. The mixture was stirred at room temperature for 30 min and then filtered. The filtrate was concentrated to give a crude diol. To a solution of this crude diol in ether (1000 ml) was added formic acid (1000 ml) at −10°C. After the reaction solution was stirred at −10°C for 10 min, EtOAc and H_2O were added. The organic solution was separated, washed with a sat. aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/1) gave triol **13** (7.68 g, 0.018 mol, 69%) as a colorless oil. $[\alpha]_D^{20} = -32.3$ (*c* 1.74, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.97–1.07 (21H, m, *iso*-Pr), 1.18 (1H, ddd, *J* = 14.2, 8.8, 2.9 Hz, 3-H*H*), 1.52 (1H, ddd, *J* = 14.2, 9.8, 4.4 Hz, 3-*H*H), 2.15 (1H, br. s, OH), 2.29 (1H, m, 4-H), 2.90–3.15 (2H, br., OH), 3.41 (1H, dd, *J* = 10.7, 7.3 Hz), 3.48 (1H, dd, *J* = 10.7, 5.4 Hz), 3.56 (1H, br. d, *J* = 10.7 Hz), 3.72 (1H, dd, *J* = 10.7, 6.4 Hz), 3.80 (1H, m, 2-H), 4.87 (1H, d, *J* = 4.9 Hz, ArCHOTIPS), 5.96 (2H, s, OCH_2O), 6.73–6.78 (2H, m, ArH), 6.86 (1H, s, ArH). NMR δ_C ($CDCl_3$): 12.3, 17.9, 18.0, 31.8, 44.4, 63.4, 67.0, 70.1, 78.0, 101.0, 107.5, 107.7, 120.4, 135.7, 146.8, 147.4. IR ν_{max} ($CHCl_3$): 3629, 2946, 2869, 1505, 1489, 1443, 1242, 1084, 1042 cm^{-1}. *Anal.* Found: C, 61.70; H, 8.96%. Calcd. for $C_{22}H_{38}O_6Si$: C, 61.94; H, 8.98%.

*(3R)-3-[(S)-(3,4-Methylenedioxyphenyl)(triisopropylsilyloxy)methyl]-4-butanolide (**14**).* A reaction mixture of triol **13** (3.51 g, 8.23 mmol) and $NaIO_4$ (1.93 g, 9.04 mmol) in MeOH (30 ml) was stirred at room temperature for 2 h. After its concentration, the resulting residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave a crude hemiacetal. A reaction mixture of this crude hemiacetal and Ag_2CO_3-celite (9.04 g, containing *ca.* 9.04 mmol of Ag_2CO_3) in toluene (80 ml) was heated under reflux for 1 h. After the mixture was filtered, the filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc/hexane = 1/4) to give lactone **14** (2.28 g, 5.81 mmol, 71%) as a colorless oil. $[\alpha]_D^{20} = -49.5$ (*c* 1.56, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.96–1.04 (21H, m, *iso*-Pr), 2.54 (1H, dd, *J* = 17.6, 8.8 Hz, 2-*H*H), 2.62 (1H, dd, *J* = 17.6, 7.8 Hz, 2-H*H*), 2.85 (1H, m, 3-H), 4.09 (1H, dd, *J* = 9.3, 6.8 Hz, 4-*H*H), 4.15 (1H, dd, *J* = 9.3, 7.8 Hz, 4-H*H*), 4.69 (1H, d, *J* = 6.3 Hz, ArCHOTIPS), 5.97 (1H, d, *J* = 3.9 Hz, OC*H*HO), 5.97 (1H, d, *J* = 3.9 Hz, OCH*H*O), 6.71 (1H, dd, *J* = 7.8, 1.5 Hz, ArH), 6.76 (1H, d, *J* = 7.8 Hz, ArH), 6.81 (1H, d, *J* = 1.5 Hz, ArH). NMR δ_C ($CDCl_3$): 12.4, 17.9, 18.0, 31.0, 44.5, 69.5, 75.5, 101.1, 106.7, 108.0, 119.8, 135.9, 147.4, 147.9, 176.8. IR ν_{max} ($CHCl_3$): 3013, 2880, 1763, 1505, 1491, 1449, 1252, 1240, 1184, 1096, 1080, 1042 cm^{-1}. *Anal.* Found: C, 64.19; H, 8.39%. Calcd. for $C_{21}H_{32}O_5Si$: C, 64.25; H, 8.22%.

*(2S,3R)-2-[(S)-(Hydroxy)(3,4-methylenedioxyphenyl)methyl]-3-[(S)-(3,4-methylenedioxyphenyl)(triisopropylsilyloxy)methyl]-4-butanolide (**15**).* To a solution of KHMDS (20.0 ml, 0.5 M in toluene, 10.0 mmol) in THF (80 ml) was added a solution of lactone 14 (2.50 g, 6.37 mmol) in THF (20 ml) at −75°C. After stirring at −75°C for 15 min, piperonal (1.50 g, 9.99 mmol) in THF (10 ml) was added. The reaction solution was stirred at −75°C for 1 h, and then a sat. aq. NH_4Cl solution was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave *erythro* aldol product **15** (2.90 g, 5.34 mmol, 84%) as a colorless oil. $[\alpha]_D^{20} = +20.9$ (*c* 2.15, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.85–1.00 (21H, m, *iso*-Pr), 2.61 (1H, d, *J* = 3.9 Hz, OH), 2.75 (1H, dd, *J* = 4.9, 2.9 Hz, 2-H), 2.85 (1H, m, 3-H), 4.32 (1H, dd, *J* = 9.0, 4.6 Hz, 4-*H*H), 4.38 (1H, dd, *J* = 9.0, 8.3 Hz, 4-H*H*), 4.63 (1H, d, *J* = 4.4 Hz, ArCHOTIPS), 5.22 (1H, dd, *J* = 3.9, 2.9 Hz, ArC*H*OH), 5.93 (2H, s, OCH_2O), 5.96 (1H, d, *J* = 7.1 Hz, OC*H*HO), 5.97 (1H, d, *J* = 7.1 Hz, OCH*H*O), 6.42 (1H, dd, *J* = 7.8, 1.5 Hz, ArH), 6.45 (1H, d, *J* = 1.5 Hz, ArH), 6.61 (1H, d, *J* = 7.8 Hz, ArH), 6.67–6.70 (3H, m, ArH). NMR δ_C ($CDCl_3$): 12.5, 17.9, 18.0, 43.0, 48.9, 70.0, 72.7, 75.6, 101.1 (C × 2), 106.0, 106.5, 107.7, 108.0, 118.6, 119.5, 134.8, 135.1, 146.9, 147.5, 147.7, 178.4. IR ν_{max} ($CHCl_3$): 3611, 2926, 1761, 1505, 1491, 1445, 1254, 1242, 1196, 1084, 1067, 1042 cm^{-1}. *Anal.* Found: C, 63.92; H, 6.86%. Calcd. for $C_{29}H_{38}O_8Si$: C, 64.18; H, 7.06%.

*(2S,3R)-2-[(S)-(Methoxymethoxy)(3,4-methylenedioxyphenyl)methyl]-3-[(S)-(3,4-methylenedioxyphenyl)(triisopropylsilyloxy)methyl]-4-butanolide (**16**).* A reaction mixture of alcohol **15** (2.56 g, 4.72 mmol), DIPEA (12.8 ml, 73.5 mmol), and MOMCl (2.80 ml, 36.9 mmol) in CH_2Cl_2 (5 ml) was stirred at room temperature for 16 h before the additons of MeOH, H_2O, and CH_2Cl_2. The organic solution was separated, washed with 1 M aq. HCl solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave MOM ether **16** (2.77 g, 4.72 mmol, 100%) as colorless crystals, mp 108–109°C (MeOH). $[\alpha]_D^{20} = -40.0$ (*c* 3.57, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.90–1.00 (21H, m, *iso*-Pr), 2.72 (1H, dd, *J* = 3.9, 2.9 Hz, 2-*H*), 2.90 (1H, m, 3-*H*), 3.32 (3H, s, OCH_3), 4.36 (1H, dd, *J* = 9.0, 3.6 Hz, 4-*H*H), 4.46 (1H, dd, *J* = 9.0, 6.1 Hz, 4-H*H*), 4.52 (2H, s, OCH_2OCH_3), 4.65 (1H, d, *J* = 3.9 Hz, ArC*H*OTIPS), 5.17 (1H, d, *J* = 2.4 Hz, Ar-

CHOMOM), 5.92–5.98 (4H, m, OCH_2O), 6.35–6.37 (2H, m, ArH), 6.57–6.59 (2H, m, Ar*H*), 6.62 (1H, d, *J* = 7.8 Hz, Ar*H*), 6.69 (1H, d, *J* = 7.8 Hz, Ar*H*). NMR δ_C ($CDCl_3$): 12.5, 17.9, 43.0, 48.4, 56.0, 70.1, 75.8 (C × 2), 94.3, 101.1, 101.2, 106.4, 106.5, 107.6, 108.1, 119.4, 132.3, 134.9, 146.8, 147.1, 147.4, 147.8, 177.7. IR ν_{max} ($CHCl_3$): 2548, 2869, 1765, 1505, 1489, 1445, 1252, 1242, 1100, 1042, 1026 cm^{-1}. *Anal.* Found: C, 63.39; H, 7.13%. Calcd. for $C_{31}H_{42}O_9Si$: C, 63.46; H, 7.22%.

(2R,3R)-2-[(S)-(Hydroxy)(3,4-methylenedioxyphenyl)methyl]-3-[(S)-(methoxymethoxy)(3,4-methylenedioxyphenyl)methyl]butane-1,4-diol (17). To an ice-cooled suspension of $LiAlH_4$ (0.18 g, 4.74 mmol) in THF (10 ml) was added a solution of lactone **16** (2.80 g, 4.77 mmol) in THF (20 ml). The resulting reaction mixture was stirred at 0°C for 30 min before additions of a sat. aq. $MgSO_4$ solution and K_2CO_3. After stirring at room temperature for 30 min, the mixture was filtered, and the resulting filtrate was concentrated to give a crude diol. To an ice-cooled solution of this crude diol in THF (30 ml) was added (*n*-Bu)$_4$NF (5.25 ml, 1 M in THF, 5.25 mmol). After the reaction solution was stirred at 0°C for 1 h, a sat. aq. NH_4Cl solution was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/1) gave triol **17** (1.56 g, 3.59 mmol, 75%) as colorless crystals, mp 93–94°C (MeOH/*iso*-Pr_2O = 1/4). $[\alpha]_D^{20} = -129$ (*c* 1.22, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.21 (1H, m), 2.34 (1H, m), 3.33 (3H, s, OCH_3), 3.60 (1H, dd, *J* = 10.2, 8.3 Hz), 3.72–3.79 (2H, m), 3.89 (1H, dd, *J* = 10.2, 4.6 Hz), 3.91–4.09 (3H, br.), 4.46 (2H, s, OCH_2OCH$_3$), 4.72 (1H, d, *J* = 6.4 Hz, ArC*H*OH), 4.91 (1H, d, *J* = 5.4 Hz, ArCHOMOM), 5.92–5.95 (4H, m, OCH_2O), 6.56–6.60 (4H, m, ArH), 6.63–6.67 (2H, m, ArH). NMR δ_C ($CDCl_3$): 44.2, 45.0, 56.3, 61.3, 61.6, 73.8, 78.2, 94.4, 100.9, 101.0, 106.3, 107.0, 107.7, 107.8, 119.0, 120.6, 133.4, 137.1, 146.4, 147.0, 147.4, 147.7. IR ν_{max} ($CHCl_3$): 3420, 2869, 1505, 1489, 1445, 1242, 1042 cm^{-1}. *Anal.* Found: C, 60.82; H, 6.03%. Calcd. for $C_{22}H_{26}O_9$: C, 60.93; H, 6.08%.

(2S,4S)-2-[(R)-(3,4-Methylenedioxyphenyl)(triisopropylsilyloxy)methyl]-5-trityloxy-4-pentanolide (18). To an ice-cooled solution of *threo*-**11** (10.3 g, 0.020 mol) and 2,6-lutidine (5.16 ml, 0.045 mol) in CH_2Cl_2 (100 ml) was added TIPSOTf (5.96 ml, 0.022 mol). The reaction solution was stirred at 0°C for 1 h before addition of sat. aq. $NaHCO_3$ solution. The organic solution was separated, washed with a sat. aq. $CuSO_4$ solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/19) gave silyl ether **18** (12.1 g, 0.018 mol, 90%) as colorless crystals, mp 118–119°C (*iso*-Pr_2O). $[\alpha]_D^{20} = +20.4$ (*c* 1.18, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.98–1.02 (18H, m, CH(CH_3)$_2$), 1.05–1.16 (3H, m, C*H*(CH_3)$_2$), 2.06 (1H, ddd, *J* = 13.4, 10.3, 5.4 Hz, 3-*H*H), 2.23 (1H, ddd, *J* = 13.4, 8.3, 6.7 Hz, 3-H*H*), 2.94 (1H, dd, *J* = 10.7, 3.9 Hz, 5-*H*H), 3.34 (1H, dd, *J* = 10.7, 2.9 Hz, 5-H*H*), 3.41 (1H, ddd, *J* = 10.3, 6.7, 3.9 Hz, 2-H), 3.94 (1H, m, 4-H), 5.40 (1H, d, *J* = 3.9 Hz, ArCHOTIPS), 5.94 (2H, s, OCH_2O), 6.74 (1H, d, *J* = 7.8 Hz, ArH), 6.85 (1H, dd, *J* = 7.8, 1.5 Hz, ArH), 6.91 (1H, d, *J* = 1.5 Hz, ArH), 7.20–7.30 (9H, m, ArH), 7.38–7.43 (6H, m, ArH). NMR δ_C ($CDCl_3$): 12.2, 17.9, 18.0, 24.3, 49.5, 65.1, 72.9, 77.8, 86.9, 101.0, 107.3, 107.9, 120.0, 127.1, 127.9, 128.6, 134.2, 143.5, 147.1, 147.5, 176.8. IR ν_{max} ($CHCl_3$): 3036, 2946, 2869, 1763, 1505, 1489, 1449, 1254, 1240, 1199, 1100, 1092, 1042, 1017 cm^{-1}. *Anal.* Found: C, 74.03; H, 7.35%. Calcd. for $C_{41}H_{48}O_6Si$: C, 74.06; H, 7.28%.

(2S,4R)-4-[(R)-(3,4-Methylenedioxyphenyl)(triisopropylsilyloxy)methyl]pentane-1,2,5-triol (19). To an ice-cooled suspension of $LiAlH_4$ (0.68 g, 0.018 mol) in THF (10 ml) was added a solution of lactone **18** (12.1 g, 0.018 mol) in THF (60 ml). The reaction mixture was stirred at 0°C for 1 h before additions of a sat. aq. $MgSO_4$ solution and K_2CO_3. The mixture was stirred at room temperature for 30 min and filtered. The resulting filtrate was concentrated to give a crude diol. To a solution of this crude diol in ether (900 ml) was added formic acid (900 ml) at −10°C. After the reaction solution was stirred at −10°C for 10 min, EtOAc and H_2O were added. The organic solution was separated, washed with a sat. aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/1) gave triol **19** (4.69 g, 0.011 mol, 61%) as a colorless oil. $[\alpha]_D^{20} = +21.8$ (*c* 1.10, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.96–1.03 (21H, m, *iso*-Pr), 1.33 (1H, ddd, *J* = 14.5, 8.1, 2.9 Hz, 3-*H*H), 1.50 (1H, ddd, *J* = 14.5, 9.4, 4.9 Hz, 3-H*H*), 2.11 (1H, m, 4-H), 2.38 (1H, br. s, OH), 2.77 (1H, br. s, OH), 3.42 (1H, br. dd, *J* = 8.8, 8.3 Hz), 3.50–3.58 (2H, m), 3.62 (1H, dd, *J* = 11.2, 5.9 Hz), 3.67 (1H, dd, *J* = 10.7, 4.9 Hz), 3.79 (1H, m, 2-H), 4.90 (1H, d, *J* = 5.4 Hz, ArCHOTIPS), 5.95 (2H, s, OCH_2O), 6.73–6.77 (2H, m, ArH), 6.86 (1H, s, ArH). NMR δ_C ($CDCl_3$): 12.4, 17.9, 18.0, 31.2, 45.5, 63.2, 67.0, 70.3, 77.2, 100.9, 107.5, 107.7, 120.3, 136.3, 146.8, 147.5. IR ν_{max} ($CHCl_3$): 3400, 2946, 2869, 1505, 1489, 1442, 1244, 1090, 1042, 884 cm^{-1}. *Anal.* Found: C, 62.04; H, 9.02%. Calcd. for $C_{22}H_{38}O_6Si$: C, 61.94; H, 8.98%.

(3R)-3-[(R)-(3,4-Methylenedioxyphenyl)(triisopropylsilyloxy)methyl]-4-butanolide (20). A reaction mixture of triol **19** (2.30 g, 5.39 mmol) and $NaIO_4$ (1.27 g, 5.94 mmol) in MeOH (30 ml) was

stirred at room temperature for 2 h. After its concentration, the resulting residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave a crude hemiacetal. A reaction mixture of this crude hemiacetal and Ag_2CO_3-celite (5.86 g, containing *ca.* 5.86 mmol of Ag_2CO_3) in toluene (80 ml) was heated under reflux for 1 h. After the mixture was filtered, the filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc/hexane = 1/4) to give lactone **20** (2.10 g, 5.35 mmol, 99%) as a colorless oil. $[\alpha]_D^{20} = +49.3$ (*c* 1.02, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.95–1.00 (21H, m, *iso*-Pr), 2.29 (1H, dd, $J = 17.6$, 8.3 Hz, 2-*H*H), 2.34 (1H, dd, $J = 17.6$, 8.3 Hz, 2-*H*H), 2.82 (1H, m, 3-H), 4.34 (1H, dd, $J = 9.3$, 7.3 Hz, 4-*H*H), 4.37 (1H, dd, $J = 9.3$, 6.8 Hz, 4-H*H*), 4.64 (1H, d, $J = 6.8$ Hz, ArCHOTIPS), 5.97 (2H, s, OCH_2O), 6.72 (1H, d, $J = 7.8$ Hz, ArH), 6.76 (1H, d, $J = 7.8$ Hz, ArH), 6.79 (1H, s, ArH). NMR δ_C ($CDCl_3$): 12.5, 17.9, 18.0, 31.1, 44.7, 70.3, 75.8, 101.1, 106.6, 108.0, 119.9, 136.2, 147.4, 147.9, 176.6. IR ν_{max} ($CHCl_3$): 2948, 2869, 1775, 1505, 1489, 1445, 1244, 1179, 1103, 1084, 1042, 1015, 884 cm^{-1}. *Anal.* Found: C, 64.50; H, 8.33%. Calcd. for $C_{21}H_{32}O_5Si$: C, 64.25; H, 8.22%.

(2S,3R)-2-[(S)-(Hydroxy)(3,4-methylenedioxyphenyl)methyl]-3-[(R)-(3,4-methylenedioxyphenyl)(triisopropylsilyloxy)methyl]-4-butanolide (21). To a solution of KHMDS (16.0 ml, 0.5 M in toluene, 8.00 mmol) in THF (80 ml) was added a solution of lactone **20** (2.10 g, 5.35 mmol) in THF (20 ml) at −75°C. After stirring at −75°C for 15 min, piperonal (1.21 g, 8.03 mmol) in THF (10 ml) was added. The reaction solution was stirred at −75°C for 1 h, and then a sat. aq. NH_4Cl solution was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave *erythro* aldol product **21** (2.50 g, 4.61 mmol, 86%) as a colorless oil. $[\alpha]_D^{20} = +23.6$ (*c* 1.27, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.87–0.93 (21H, m, *iso*-Pr), 2.54 (1H, dd, $J = 3.4$, 3.4 Hz, 2-H), 2.64 (1H, d, $J = 4.4$ Hz, OH), 2.72 (1H, m, 3-H), 4.26 (1H, d, $J = 7.3$ Hz, ArCHOTIPS), 4.32 (1H, dd, $J = 8.8$, 8.3 Hz, 4-*H*H), 4.59 (1H, dd, $J = 8.8$, 3.9 Hz, 4-H*H*), 5.16 (1H, dd, $J = 4.4$, 3.4 Hz, ArC*H*OH), 5.91–5.98 (4H, m, OCH_2O), 6.40–6.44 (2H, m, ArH), 6.56–6.60 (2H, m, ArH), 6.63 (1H, s, ArH), 6.67 (1H, d, $J = 7.8$ Hz, ArH). NMR δ_C ($CDCl_3$): 12.4, 17.8, 18.0, 43.8, 50.6, 69.6, 72.6, 75.5, 101.1, 101.2, 105.8, 106.5, 107.4, 107.9, 118.4, 119.9, 134.8, 135.7, 146.9, 147.0, 147.5, 147.7, 178.5. IR ν_{max} ($CHCl_3$): 3500, 2948, 2869, 1759, 1505, 1489, 1445, 1244, 1096, 1042 cm^{-1}. *Anal.* Found: C, 64.39; H, 7.23%. Calcd. for $C_{29}H_{38}O_8Si$: C, 64.18; H, 7.06%.

(2S,3R)-2-[(S)-(Methoxymethoxy)(3,4-methylenedioxyphenyl)methyl]-3-[(R)-(3,4-methylenedioxyphenyl)(triisopropylsilyloxy)methyl]-4-butanolide (22). A reaction mixture of alcohol **21** (2.50 g, 4.61 mmol), DIPEA (12.9 ml, 74.1 mmol), and MOMCl (2.80 ml, 36.9 mmol) in CH_2Cl_2 (5 ml) was stirred at room temperature for 16 h before additions of MeOH, H_2O, and CH_2Cl_2. The organic solution was separated, washed with a 1 M aq. HCl solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave MOM ether **22** (2.21 g, 3.77 mmol, 82%) as a colorless oil. $[\alpha]_D^{20} = -43.8$ (*c* 0.80, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.87–0.96 (21H, m, *iso*-Pr), 2.47 (1H, dd, $J = 3.4$, 2.9 Hz, 2-H), 2.79 (1H, m, 3-H), 3.32 (3H, s, OCH_3), 4.24 (1H, d, $J = 7.8$ Hz, ArCHOTIPS), 4.37 (1H, dd, $J = 8.8$, 7.8 Hz, 4-*H*H), 4.52 (2H, s, OCH_2OCH_3), 4.64 (1H, dd, $J = 8.9$, 3.2 Hz, 4-H*H*), 5.14 (1H, d, $J = 2.4$ Hz, ArCHOMOM), 5.90–5.99 (4H, m, OCH_2O), 6.37 (1H, s, ArH), 6.40 (1H, d, $J = 8.3$ Hz, ArH), 6.51–6.56 (2H, m, ArH), 6.60 (1H, s, ArH), 6.66 (1H, d, $J = 7.8$ Hz, ArH). NMR δ_C ($CDCl_3$): 12.4, 17.8, 17.9, 43.9, 50.4, 56.1, 69.4, 75.4, 75.9, 94.3, 101.1, 101.2, 106.3, 106.4, 107.2, 108.1, 119.2, 120.3, 131.9, 135.6, 147.0, 147.1, 147.5, 147.8, 177.8. IR ν_{max} ($CHCl_3$): 2948, 1767, 1732, 1505, 1489, 1445, 1248, 1100, 1042, 1026, 909 cm^{-1}. *Anal.* Found: C, 63.48; H, 6.92%. Calcd. for $C_{31}H_{42}O_9Si$: C, 63.46; H, 7.22%.

(2R,3R)-2-[(R)-(Hydroxy)(3,4-methylenedioxyphenyl)methyl]-3-[(S)-(methoxymethoxy)(3,4-methylenedioxyphenyl)methyl]butane-1,4-diol (23). To a solution of lactone **22** (2.11 g, 3.60 mmol) in toluene (20 ml) was added DIBAL-H (3.84 ml, 1 M in toluene, 3.84 mmol) at −75°C. After stirring at −75°C for 1 h, a 1 M aq. HCl solution was added. The organic solution was separated, washed with a sat. aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Concentration gave a crude hemiacetal. To an ice-cooled solution of this crude hemiacetal in EtOH (20 ml) was added $NaBH_4$ (0.15 g, 3.97 mmol). The reaction mixture was stirred at room temperature for 2 h before addition of a 1 M aq. HCl solution. After neutralization with a sat. aq. $NaHCO_3$ solution, the mixture was concentrated. The resulting 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 THF (20 ml) was added (n-Bu)$_4$NF (3.80 ml, 1 M THF, 3.80 mmol). The reaction solution was stirred at 0°C for 1 h before addition of a sat. aq. NH_4Cl solution. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/1) gave triol **23** (1.56 g, 3.59 mmol, 100%) as a

colorless oil. $[\alpha]_D^{20} = -116$ (*c* 0.76, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.75–1.88 (3H, m), 2.39 (1H, m), 3.32 (3H, s, OCH_3), 3.45 (1H, ddd, *J* = 11.5, 4.6 Hz), 3.50 (1H, br. s, OH), 3.74 (1H, dd, *J* = 11.5, 3.7 Hz), 3.93 (1H, dd, *J* = 11.7, 2.5 Hz), 4.04 (1H, dd, *J* = 11.7, 4.4 Hz), 4.45 (2H, s, OCH_2OCH_3), 4.73 (1H, d, *J* = 7.8 Hz, ArCHOR), 4.77 (1H, d, *J* = 7.3 Hz, ArCHOR), 5.94 (2H, s, OCH_2O), 5.95 (2H, s, OCH_2O), 6.66–6.67 (3H, m, ArH), 6.69–6.73 (3H, m, ArH). NMR δ_C ($CDCl_3$): 44.1, 47.6, 56.1, 59.5, 60.4, 76.3, 77.4, 94.4, 101.0 (C × 2), 106.7, 107.2, 107.9, 120.0, 120.9, 133.7, 137.0, 146.9, 147.1, 147.8. IR ν_{max} ($CHCl_3$): 3375, 2894, 1505, 1489, 1443, 1246, 1042 cm^{-1}. HRMS (FAB) *m/z* ($M^+ - H$): calcd. for $C_{22}H_{25}O_9$, 433.1498; found, 433.1499.

(2S,3R,4R)-3-Hydroxymethyl-4-[(S)-(methoxymethoxy)(3,4-methylenedioxyphenyl)methyl]-2-(3,4-methylenedioxyphenyl)tetrahydrofuran (24). 1) A reaction solution of triol **17** (1.20 g, 2.76 mmol) and CSA (10 mg, 0.043 mmol) in CH_2Cl_2 (5 ml) was stood at 3°C for 4 h before addition of a few drops of Et_3N. Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/2) gave tetrahydrofuran derivative **24** (0.70 g, 1.68 mmol, 61%) as colorless crystals, mp 73–74°C (*iso*-Pr_2O). 2) A reaction solution of triol **23** (0.10 g, 0.23 mmol) and CSA (3 mg, 0.013 mmol) in CH_2Cl_2 (5 ml) was stood at 3°C for 40 h before addition of a few drops of Et_3N. Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/2) gave tetrahydrofuran derivative **24** (54 mg, 0.13 mmol, 57%) as colorless crystals, mp 73–74°C (*iso*-Pr_2O). $[\alpha]_D^{20} = -106$ (*c* 0.82, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.51 (1H, m), 2.83 (1H, m), 3.08 (1H, dd, *J* = 9.0, 3.9 Hz, OH), 3.41 (1H, dd, *J* = 8.8, 6.3 Hz, 5-*H*H), 3.41 (3H, s, OCH_3), 3.70 (1H, dd, *J* = 8.8, 7.3 Hz, 5-H*H*), 3.76 (1H, ddd, *J* = 11.2, 9.0, 5.4 Hz, C*H*HOH), 3.98 (1H, ddd, *J* = 11.2, 7.8, 3.9 Hz, CH*H*OH), 4.45 (1H, d, *J* = 6.4 Hz, OC*H*HOCH$_3$), 4.48 (1H, d, *J* = 6.4 Hz, CH*H*OCH$_3$), 4.71 (1H, d, *J* = 10.7 Hz, ArCHOMOM), 4.74 (1H, d, *J* = 7.8 Hz, 2-H), 5.94 (2H, s, OCH_2O), 5.98 (2H, s, OCH_2O), 6.76 (4H, s, ArH), 6.79–6.83 (2H, s, ArH). NMR δ_C ($CDCl_3$): 47.2, 52.6, 56.8, 60.3, 70.4, 82.8, 94.0, 101.0, 101.2, 106.3, 107.2, 108.1, 119.2, 121.6, 133.3, 136.3, 144.8. IR ν_{max} ($CHCl_3$): 3500, 2894, 1505, 1489, 1445, 1244, 1042 cm^{-1}. *Anal.* Found: C, 63.55; H, 6.11%. Calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81%.

(2S,3S,4R)-4-[(S)-(Methoxymethoxy)(3,4-methylenedioxyphenyl)methyl]-2-(3,4-methylenedioxyphenyl)-3-tetrahydrofurancarbaldehyde (25). A reaction mixture of alcohol **24** (0.61 g, 1.46 mmol) and PCC (0.35 g, 1.62 mmol), and MS 4A (0.1 g) in CH_2Cl_2 (20 ml) was stirred at room temperature for 7 h before addition of dry ether. The resulting mixture was filtered, and the resulting filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc/hexane = 1/9) to give aldehyde **25** (0.44 g, 1.06 mmol, 73%) as a colorless oil. $[\alpha]_D^{20} = -77.7$ (*c* 4.00, $CHCl_3$). NMR δ_H ($CDCl_3$): 3.13 (1H, m, 4-H), 3.24 (1H, ddd, *J* = 8.6, 6.8, 2.4 Hz, 3-H), 3.29 (3H, s, OCH_3), 3.58 (1H, dd, *J* = 9.3, 7.3 Hz, 5-*H*H), 3.79 (1H, dd, *J* = 9.3, 6.8 Hz, 5-H*H*), 4.37 (1H, d, *J* = 6.8 Hz, OC*H*HOCH$_3$), 4.42 (1H, d, *J* = 6.8 Hz, OCH*H*OCH$_3$), 4.53 (1H, d, *J* = 10.3 Hz, ArCHOMOM), 5.32 (1H, d, *J* = 6.8 Hz, 2-H), 5.93 (2H, s, OCH_2O), 5.97 (1H, d, *J* = 2.9 Hz, OC*H*HO), 5.97 (1H, d, *J* = 2.9 Hz, OCH*H*O), 6.74–6.77 (4H, m, ArH), 6.80–6.81 (2H, m, ArH), 10.06 (1H, d, *J* = 2.4 Hz, CHO). NMR δ_C ($CDCl_3$): 50.3, 56.8, 61.7, 70.4, 76.4, 80.1, 94.2, 101.0, 101.2, 106.2, 107.0, 108.2, 108.3, 119.0, 121.4, 133.0, 135.4, 147.1, 147.8, 148.3, 200.0. IR ν_{max} ($CHCl_3$): 2894, 1717, 1505, 1489, 1447, 1244, 1098, 1042 cm^{-1}. *Anal.* Found: C, 63.72; H, 5.59%. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.53%.

(1R,2S,4R/S,5S,6S)-4-Hydroxy-2,6-bis(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (26). A reaction solution of MOM ether **25** (0.30 g, 0.72 mmol) in THF (10 ml) and a 6 M aq. HCl solution (15 ml) was stirred at room temperature for 5 h before addition of EtOAc. The organic solution was separated, washed with sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave hemiacetal **26** (0.22 g, 0.59 mmol, 82%) as colorless crystals, mp 158–159°C (MeOH). $[\alpha]_D^{20} = +32.1$ (*c* 1.84, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.90 (0.7H, d, *J* = 3.4 Hz, OH), 2.95 (1H, m), 3.20 (0.7H, m), 3.27 (0.3H, m), 3.95 (0.3H, dd, *J* = 8.5, 3.9 Hz, 8-*H*H), 4.01(0.7H, dd, *J* = 9.3, 3.4 Hz, 8-H*H*), 4.05 (0.3H, dd, *J* = 8.5, 6.4 Hz, 8-*H*H), 4.24 (0.7H, dd, *J* = 9.3, 5.9 Hz, 8-H*H*), 4.83 (1H, d, *J* = 7.3 Hz, ArC*H*OCH$_2$), 4.95–4.97 (0.3H, br., OH), 4.96 (1H, d, *J* = 6.8 Hz, ArC*H*OCH$_2$), 5.58 (0.7H, d, *J* = 2.9 Hz, 4-H), 5.78 (0.3H, dd, *J* = 5.9, 5.4 Hz, 4-H), 5.96 (4H, s, OCH_2O), 6.77–6.88 (5H, m, ArH), 7.04 (1H, s, ArH). NMR δ_C ($CDCl_3$): 53.1, 54.2, 57.3, 62.0, 70.5, 72.2, 79.6, 83.2, 83.7, 88.0, 98.3, 101.0, 101.6, 106.2, 106.3, 106.6, 107.0, 108.0, 108.1, 108.2, 119.1, 119.2, 119.5, 120.0, 134.7, 135.3, 136.0, 147.2, 147.3, 147.8, 148.0. IR ν_{max} ($CHCl_3$): 3400, 3013, 2890, 1505, 1489, 1447, 1248, 1042 cm^{-1}. *Anal.* Found: C, 64.48; H, 5.25%. Calcd. for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90%.

(1R,2S,5S,6S)-2,6-Bis(3,4-methylenedioxyphenyl)-4-oxo-3,7-dioxabicyclo[3.3.0]octane ((+)-aptosimon **1**). A reaction mixture of hemiacetal **26** (40 mg, 0.11 mmol) and PCC (26 mg, 0.12 mmol), and MS 4A (10 mg) in CH_2Cl_2 (5 ml) was stirred at room temperature for 3 h before addition of dry ether. The mixture was filtered, and the resulting

filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc/hexane = 1/3) to give (+)-aptosimon (**1**) (34 mg, 0.092 mmol, 84%) as colorless crystals, mp 122–123 °C (*iso*-Pr_2O) (lit.[1] 123 °C). $[\alpha]_D^{20} = +69.2$ (*c* 0.65, $CHCl_3$), lit[1] $[\alpha]_D^{20} = +70$ (*c* 2.0, $CHCl_3$). NMR δ_H ($CDCl_3$): 3.20 (1H, m, 1-H), 3.42 (1H, dd, $J = 9.0$, 3.4 Hz, 5-H), 4.00 (1H, dd, $J = 9.6$, 4.9 Hz, 8β-H), 4.32 (1H, dd, $J = 9.6$, 6.8 Hz, 8α-H), 5.28 (1H, d, $J = 3.9$ Hz, 2-H), 5.30 (1H, d, $J = 3.4$ Hz, 6-H), 5.95 (2H, s, OCH_2O), 5.97 (2H, s, OCH_2O), 6.75–6.79 (4H, m, ArH), 6.80–6.86 (2H, m, ArH). NMR δ_C ($CDCl_3$): 49.9, 53.2, 72.6, 83.3, 84.3, 101.1, 101.4, 105.7, 105.9, 108.3, 108.5, 118.7, 118.8, 119.0, 133.0, 134.3, 147.2, 148.0, 148.3, 176.6. IR ν_{max} ($CHCl_3$): 3013, 2890, 1771, 1507, 1491, 1447, 1252, 1184, 1042 cm^{-1}. HRMS (FAB) *m/z* (M^+): calcd. for $C_{20}H_{16}O_7$, 368.0896; found, 368.0901.

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