Enantioselective Synthesis of the Tetrahydrofuran Lignans (–)- and (+)-Magnolone

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The optically pure trisubstituted 7′-oxotetrahydrofuran lignans (−)- and (+)-magnolone (**1**) were synthesized by employing stereoselective S_N1 intramolecular cyclization as a key reaction. The absolute configuration of naturally occurring (−)-magnolone was determined as (7*S*,8*R*,8′*S*).

(−)-Magnolone (**1**), a trisubstituted 7′-oxotetrahydrofuran lignan, has been isolated from the leaves of *Magnolia coco*,[1] and its relative configuration has been proposed (Figure 1). *M. coco* has been used as an herbal remedy for the treatment of impaired liver function and cancer. There are only a few reports on the isolation of this type of lignan.[2] Trisubstituted tetrahydrofurans have interesting structures, and some researchers have developed a synthesis route to (−)-sesaminone.[3,4] It is important to synthesize an optically pure natural product and compare the specific rotation with that of the natural product. The biosynthesis of lignans is complicated, and some naturally occurring lignans are not optically pure.[5,6] Naturally occurring lignans may possess the same relative configuration, but their absolute configuration may vary depending on their plant source.[7] Tetrahydrofuran lignans are pharmacologically important compounds, so it is necessary to estimate the optical purity of the isolated compound before using it in biological research. Here we describe the synthesis of optically pure (−)- and (+)-magnolone and comparison of the specific rotation of these compounds with that of the natural compound. This is a new synthetic route to the production of trisubstituted 7′-oxotetrahydrofuran lignans.

The key reaction in our synthesis is the stereoselective S_N1 intramolecular etherification of the intermediates **2** and **3** to **4** in the presence of acid as a catalyst. There is the possibility of the competitive production of hemiacetals **5** and **6** under these reaction conditions. Since oxygen atom attack on the benzylic carbocation (Reaction Sequence 1) would be favored, the protective groups on the primary and benzylic hydroxy groups (R_1, R_2, R_3) are important in avoiding production of hemiacetals (Reaction Sequences 2 and 3) (Scheme 1). Different protective groups for the primary hydroxy groups (R_1 and R_2) require selective deprotection, thus increasing the number of steps. It would be better if the protective groups (R_1 and R_2) were identical and the S_N1 cyclization of **2** and **3** giving **4** could be carried out without deprotection.

Results and Discussion

The synthesis of the key intermediates **18** and **19** was started from the *syn*-aldol product **7**[8] (Scheme 2). The reductive removal of the auxiliary of **7** and selective protection of the resulting primary hydroxy group as trityl ether gave **8**. After oxidative cleavage of the olefin **8** by using the OsO_4 oxidation–$NaIO_4$ system, the resulting unstable hemiacetal was converted to lactone **9** by pyridinium chlorochromate oxidation. The aldol condensation of lactone **9** with piperonal by using potassium hexamethyldisilazane gave the *erythro* aldol product **10** (72%) and the *threo* aldol product **11** (21%). Since this new benzylic stereogenic center would be converted to one stereogenic center through the production of a benzylic carbocation, the *erythro* and *threo* selectivity at this stage was unimportant. The configuration of the *erythro* and *threo* isomers was determined from the coupling constant between 2-H and the benzylic proton (*erythro* **10**: 2.9 Hz, *threo* **11**: 7.3 Hz).[9] Because of its stability against hydride, which is used for the reduction of lactone, the MOM ether was selected as the protective group for the benzylic hydroxy group. After conversion of the aldol products **10** and **11** to the MOM ethers **12** and **13**, the resulting lactones were subjected to $LiAlH_4$ reduction followed by cleavage of the trityl ether in a formic acid–ether system, producing the corresponding triols **14** and **15**, respectively. Selective protection of the primary hydroxy groups as pivaloyl esters followed by pyridinium chlorochromate oxidation gave the ketones **18** and **19**, respectively.

Next, the reaction conditions required for stereoselective S_N1 cyclization of **18** and **19** were examined. Treatment of the ketone **18** with 6 M aqueous HCl solution in THF at room temperature gave the trisubstituted tetrahydrofuran **20** with the desired configuration (41%) and **21** with undesired configuration (15%). The ketone **19** gave **20** (40%) and **21** (17%) under the same reaction conditions. An NOE association was observed between 7-H and 8′-H of **20**. Employing camphorsulfonic acid in CH_2Cl_2 gave the same result. The use of *p*-toluenesulfonic acid in CH_2Cl_2 showed a decrease in stereoselectivity. The stereoselectivity for **20** was increased (99% de) at 0 °C in 6 M aqueous HCl–THF; however, the yield was decreased (22%), recovering ketone **18** (59%). A longer reaction time at 0 °C did not increase the yield. In this reaction, the attack of the 9′-oxygen on the 7-benzylic carbocation from the opposite side of the 8-substituent was favored. The formation of hemiacetals, which could be assumed to be produced as by-products (Figure 1), was not observed, and the ketone **18** or **19** was recovered. The selective cyclization was achieved without deprotection of the primary hydroxy group.

The hydrolysis of the pivaloyl ester **20** by exposure to aqueous NaOH solution gave (−)-magnolone (**1**) with a yield of 88%. (+)-Magnolone was also synthesized by the same method. The enantiomeric excess of synthesized (−)- and (+)-magnolone (**1**) was determined to be >>99% ee by employing a chiral column. The absolute configuration of natural (−)-magnolone was determined to be (7*S*,8*R*,8′*S*) by the comparison of the specific rotation of the synthesized compounds ($[\alpha]^{20}_D$ −19) with reported data ($[\alpha]^{21}_D$ −11.25).[1] This research demonstrates a new method for synthesizing trisubstituted 7′-oxotetrahydrofuran lignans.

Experimental Section

General Experimental Procedures. Melting points were uncorrected. Optical rotations were measured on a Horiba SEPA-200 instrument. IR data were measured with a Horiba FT-720 instrument. NMR data were obtained using a JNM-EX400 spectrometer. EI- and FABMS data were measured with a JMS-MS700V spectrometer. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh). HPLC analysis was performed with Shimadzu LC-6AD and SPD-6AV instruments. The numbering of compounds follows IUPAC nomenclatural rules.

(3*S*,4*R*)-4-(3,4-Dimethoxyphenyl)-3-trityloxymethyl-4-butanolide (9). To a solution of *syn*-aldol product **7**[8] (14.0 g, 32.9 mmol) and MeOH (3.07 mL, 75.8 mmol) in THF (200 mL) was added $LiBH_4$ (1.65 g,

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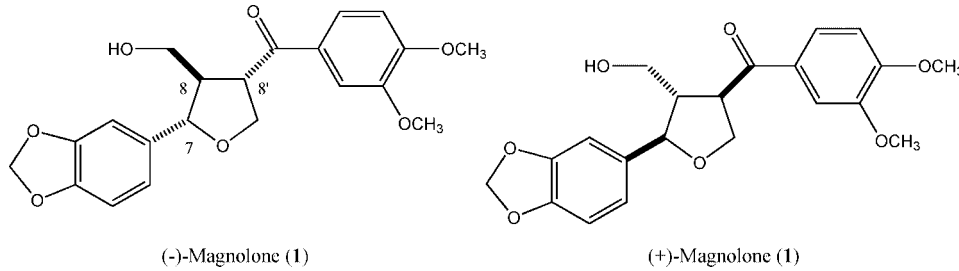
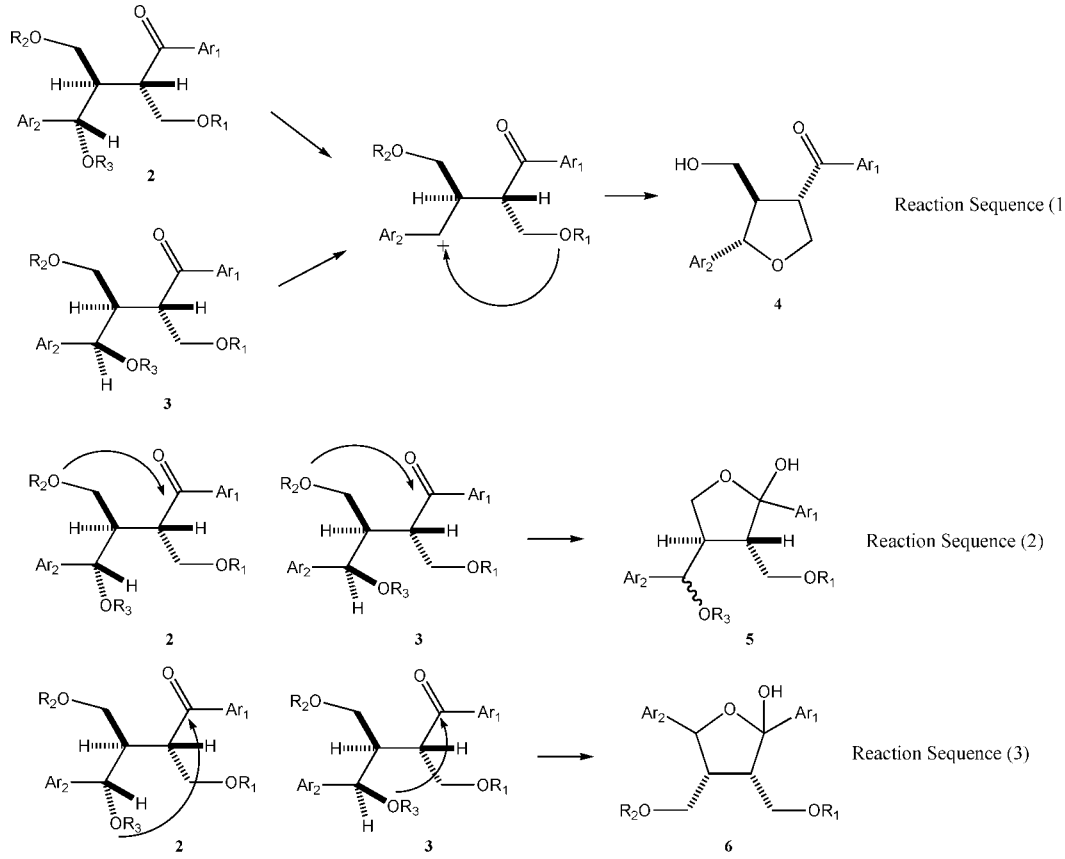


Figure 1. (−)- and (+)-Magnolone (**1**).

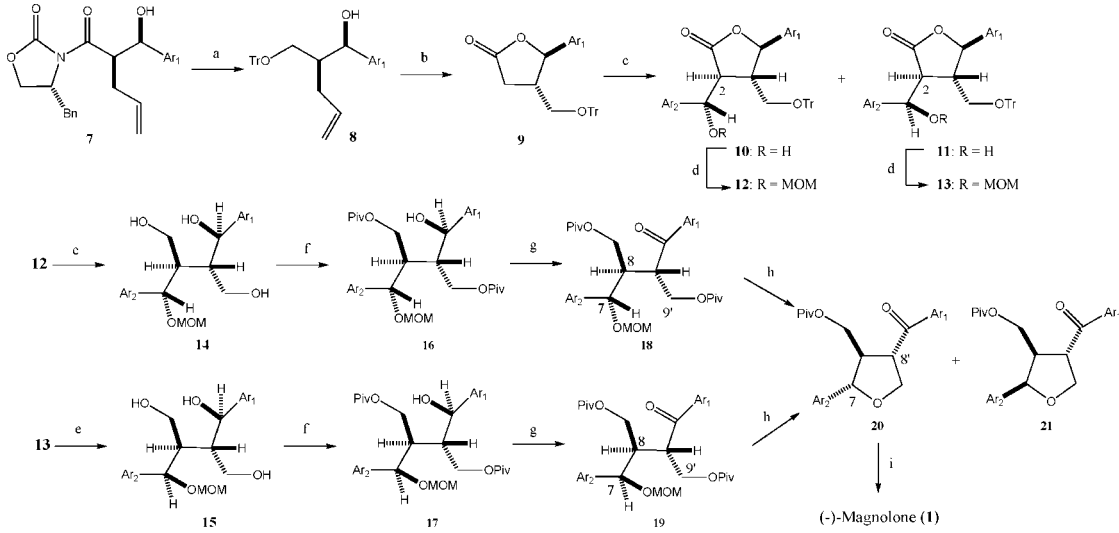
Scheme 1. Desired S_N1 Cyclization and Assumed Production of Hemiacetals as Artifacts



Ar_1 = 3,4-dimethoxyphenyl, Ar_2 = 3,4--methylenedioxyphenyl

75.8 mmol) in THF (20 mL) at 0 °C, and then the resulting reaction solution was stirred at 0 °C for 1 h before addition of 1 M aqueous NaOH solution (100 mL) at 0 °C. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration of the organic solvent gave a crude diol. A solution of the crude diol, trityl chloride (10.3 g, 36.9 mmol), and 4-DMAP (70 mg, 0.57 mmol) in pyridine (40 mL) was stirred at room temperature for 1 h before addition of H_2O and EtOAc. The organic solution was separated, washed with saturated aqueous $CuSO_4$ solution, saturatedurated aqueous $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). After evaporation of the organic solution, the residue was applied to silica gel column chromatography (EtOAc/*n*-hexane, 1:5 and 1:2) to give trityloxy olefin **8** (12.1 g, 24.5 mmol, 74%, 2 steps) as a colorless oil: $[\alpha]^{20}_D$ −1 (*c* 0.2, $CHCl_3$); IR 3500, 3010, 1259, 1139, 1029 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98 (1H, m, C *H*CH(OH)Ar), 2.14–2.26 (2H, m, CH_2═CHC *H*$_2$CH), 3.12 (1H, d, *J* = 3.2 Hz, OH), 3.20 (1H, dd, *J* = 9.4, 4.1 Hz, C*H*HOTr), 3.26 (1H, dd, *J* = 9.4, 4.1 Hz, CH*H*OTr), 3.81 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.86–4.95 (3H, m, ArC *H*OH, C*H*$_2$═CH), 5.58 (1H, m, C*H*═CH_2), 6.73–6.77 (2H, m, ArH), 6.85 (1H, s, ArH), 7.20–7.30 (9H, m, ArH), 7.40–7.42 (6H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 30.3, 45.8, 55.76, 55.82, 64.1, 75.4, 87.2, 109.4, 110.8, 116.2, 118.4, 127.0, 127.8, 128.6, 135.2, 136.9, 143.7, 147.9, 148.6; FABMS *m/z* 495 ((M + 1)$^+$, 1), 243 (100); *anal*. C 80.33%, H 6.95%, calcd for $C_{33}H_{34}O_4$, C 80.13%, H 6.93%. (+)-Trityloxy olefin **8**: $[\alpha]^{20}_D$ +1 (*c* 0.3, $CHCl_3$). A solution of (−)-trityloxy olefin **8** (12.1 g, 24.5 mmol), 4-methylmorpholine *N*-oxide (4.0 g, 34.1 mmol), and OsO_4 (aqueous 2% solution, 2.5 mL) in acetone (230 mL), *tert*-BuOH (60 mL), and H_2O (60 mL) was stirred at room temperature for 12 h before addition of saturated aqueous $Na_2S_2O_3$ 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 of the solvent gave a crude glycol. A mixture of the crude glycol and $NaIO_4$ (6.89 g, 32.2 mmol) in MeOH (100 mL) was stirred at room temperature for 1.5 h before concentration of the reaction mixture. EtOAc (200 mL) and H_2O (200 mL) were added to the residue. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Evaporation of the solvent and subsequent Si column chromatography (EtOAc/*n*-hexane, 1:3) gave an unstable hemiacetal (11.0 g, 22.2 mmol, 91%) as a colorless oil. A mixture of the hemiacetal (11.0 g, 22.3 mmol) and PCC (6.82 g, 31.6 mmol) in CH_2Cl_2 (70 mL) containing MS 4 Å (0.6 g) was stirred at room temperature for 13 h before addition of ether. After filtration, the filtrate was concentrated. The residue was applied to Si column chromatography (EtOAc/*n*-hexane, 1:3) to give lactone **9** (7.50 g, 15.2 mmol, 68%) as colorless crystals, which were recrystallized from EtOAc, mp 146–148 °C: $[\alpha]^{20}_D$ −4 (*c* 0.3, $CHCl_3$); IR 1774, 1230, 1144, 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.62–2.73 (3H, m, 2-H, 3-H), 3.26 (1H, dd, *J* = 9.7, 3.9 Hz, C*H*HOTr), 3.29 (1H, dd, *J* = 9.7, 4.7 Hz, CH*H*OTr), 3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.31 (1H, d,

Scheme 2. Synthesis of (−)-Magnolone (**1**)[a]



Ar_1 = 3,4-dimethoxyphenyl, Ar_2 = 3,4-methylenedioxyphenyl

[a] (a) (1) $LiBH_4$, MeOH, THF, below 0 °C, 1 h; (2) TrCl, 4-DMAP, pyridine, rt, 1 h (74% yield, 2 steps); (b) (1) OsO_4, NMO, aq acetone, *tert*-BuOH, rt, 12 h; (2) $NaIO_4$, MeOH, rt, 1.5 h; (3) PCC, MS 4A, CH_2Cl_2, rt, 13 h (68% yield, 3 steps); (c) KHMDS, piperonal, THF, −70 °C, 1 h (*erythro* **10**: 74% yield, *threo* **11**: 21% yield); (d) (1) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 12 h (**12**: 95%, **13**: 100% yield); (e) (1) $LiAlH_4$, 0 °C, 30 min; (2) HCO_2H, ether, 0 °C, 30 min (**14**: 54% yield, 2 steps, **15**: 66% yield, 2 steps); (f) PivCl, pyridine, rt, 11 h (**16**: 80% yield, **17**: 95% yield); (g) PCC, MS 4A, CH_2Cl_2, rt, 6 h (**18**: 68% yield, **19**: 65% yield); (h) 6 M aq HCl solution, THF, rt, 18 h (from **18**: **20** (41% yield), **21** (15% yield), from **19**: **20** (40% yield), **21** (17% yield); (i) 1 M aq NaOH solution, THF, rt, 12 h (88% yield).

J = 6.2 Hz, 4-H), 6.71 (1H, dd, J = 8.2, 1.9 Hz, ArH), 6.77 (1H, d, J = 1.9 Hz, ArH), 6.79 (1H, d, J = 8.2 Hz, ArH), 7.22–7.31 (9H, m, ArH), 7.37–7.40 (6H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 31.8, 44.6, 55.9, 62.0, 83.6, 86.8, 108.8, 110.9, 118.4, 127.2, 127.9, 128.5, 131.0, 143.4, 149.15, 149.18, 176.0; FABMS *m/z* 495 ((M + H)$^+$, 3), 243 (50), 154 (100), 136 (65); *anal.* C 77.50%, H 6.12%, calcd for $C_{32}H_{30}O_5$, C 77.71%, H 6.11%. (+)-**9**: $[\alpha]^{20}_D$ +4 (*c* 0.74, $CHCl_3$).

(2*S*,3*S*,4*R*)-4-(3,4-Dimethoxyphenyl)-2-[(*S*)-hydroxy(3,4-methylenedioxyphenyl)methyl]-3-trityloxymethyl-4-butanolide (10) and (2*S*,3*S*,4*R*)-4-(3,4-dimethoxyphenyl)-2-[(*R*)-hydroxy(3,4-methylenedioxyphenyl)methyl]-3-trityloxymethyl-4-butanolide (11). To a solution of KHMDS (8.70 mL, 0.5 M toluene solution, 4.35 mmol) in THF (20 mL) was added a solution of lactone **9** (1.80 g, 3.64 mmol) in THF (10 mL) at −70 °C. After stirring at −70 °C for 15 min, a solution of piperonal (0.63 g, 4.20 mmol) in THF (5 mL) was added. The resulting solution was stirred at −70 °C for 1 h before addition of a saturated aqueous NH_4Cl solution. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After evaporation of the solvent, the residue was applied to Si column chromatography (EtOAc/toluene, 7:93) to give *erythro* product **10** (1.74 g, 2.70 mmol, 74%) as a colorless oil and *threo* product **11** (0.51 g, 0.78 mmol, 21%) as a colorless oil. *Erythro* **10**: $[\alpha]^{20}_D$ −77 (*c* 0.2, $CHCl_3$); IR 3608, 2886, 1760, 1240, 1184, 1041 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.76 (1H, dd, J = 9.2, 5.1 Hz, C*H*HOTr), 2.84 (1H, m, 3-H), 2.89 (1H, dd, J = 9.3, 3.6 Hz, CH*H*OTr), 3.22 (1H, s, OH), 3.26 (1H, dd, J = 9.3, 2.9 Hz, 2-H), 3.76 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 5.05 (1H, d, J = 8.0 Hz, 4-H), 5.40 (1H, d, J = 2.9 Hz, ArC*H*OH), 5.88 (1H, s, OC*H*HO), 5.90 (1H, s, OCH*H*O), 6.52 (1H, dd, J = 8.2, 1.9 Hz, ArH), 6.66 (1H, d, J = 7.9 Hz, ArH), 6.70 (1H, d, J = 8.2 Hz, ArH), 7.20–7.26 (15H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 43.7, 50.2, 55.79, 55.82, 60.9, 71.0, 82.9, 86.6, 101.0, 105.9, 108.3, 109.7, 110.5, 118.5, 119.7, 127.0, 127.8, 128.5, 131.7, 135.0, 143.3, 146.8, 147.8, 149.1, 149.3, 177.3; FABMS *m/z* 645 ((M + H)$^+$, 1), 154 (100), 136 (65); *anal.* C 74.64%, H 5.74%, calcd for $C_{40}H_{36}O_8$, C 74.51%, H 5.63%. (+)-**10**: $[\alpha]^{20}_D$ +77 (*c* 0.3, $CHCl_3$). *Threo* **11**: $[\alpha]^{20}_D$ −45 (*c* 0.2, $CHCl_3$); IR 3608, 2886, 1760, 1240, 1164, 1044 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (1H, m, 3-H), 2.91–2.97 (2H, m, CH_2OTr), 3.16 (1H, dd, J = 8.6, 7.3 Hz, 2-H), 3.73 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.03 (1H, d, J = 2.4 Hz, OH), 4.95 (1H, dd, J = 7.3, 2.4 Hz, ArC*H*OH), 5.08 (1H, d, J = 8.3 Hz, 4-H), 5.88 (2H, s, OCH_2O), 6.45 (1H, d, J = 8.2 Hz, ArH), 6.51 (1H, s, ArH), 6.64 (1H, d, J = 7.9 Hz, ArH), 6.70–6.74 (2H, m, ArH), 6.84 (1H, s, ArH), 7.15–7.24 (15H, s, ArH); ^{13}C NMR ($CDCl_3$) δ 46.5, 49.7, 55.8, 55.9, 61.4, 74.0, 82.8, 87.0, 101.0, 107.0, 108.1, 109.1, 110.8, 119.1, 120.1, 127.1, 127.8, 128.5, 130.8, 133.9, 143.2, 147.4, 147.8, 149.1, 177.5; FABMS *m/z* 645 ((M + H)$^+$, 1), 154 (100), 136 (54); *anal.* C 74.85%, H 5.76%, calcd for $C_{40}H_{36}O_8$, C 74.51%, H 5.63%. (+)-**11**: $[\alpha]^{20}_D$ +44 (*c* 0.5, $CHCl_3$).

(2*S*,3*R*)-2-(3,4-Dimethoxybenzoyl)-3-[(*S*)-(methoxymethoxy)(3,4-methylenedioxy phenyl)methyl]tetramethylene dipivaloate (18). To a solution of aldol product **10** (1.42 g, 2.20 mmol) and diisopropylethylamine (28.2 mL, 0.16 mol) in CH_2Cl_2 (5 mL) was added chloromethyl methyl ether (6.15 mL, 0.081 mmol). After the reaction solution was stirred at room temperature for 12 h, MeOH (6.6 mL), CH_2Cl_2 (100 mL), and H_2O (100 mL) were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration of the solvent, the residue was applied to Si column chromatography (EtOAc/*n*-hexane, 1:3) to give MOM ether **12** (1.44 g, 2.09 mmol, 95%) as a colorless oil: $[\alpha]^{20}_D$ −121 (*c* 1.1, $CHCl_3$); IR 3026, 2958, 1766, 1241, 1182, 1095, 1027 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.77 (1H, dd, J = 9.3, 4.9 Hz, C*H*HOTr), 2.89 (1H, d, J = 9.3 Hz, CH*H*OTr), 2.96 (1H, m, 3-H), 3.25 (1H, d, J = 8.9 Hz, 2-H), 3.41 (3H, s, OCH_2OC*H*$_3$), 3.82 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.62 (1H, d, J = 6.1 Hz, OC*H*HOCH$_3$), 4.64 (1H, d, J = 6.1 Hz, OCH*H*OCH$_3$), 5.05 (1H, d, J = 7.8 Hz, 4-H), 5.38 (1H, s, ArCHOMOM), 5.90 (1H, s, OC *H*HO), 5.94 (1H, s, OCH *H*O), 6.52 (1H, d, J = 8.1 Hz, ArH), 6.69–6.78 (4H, m, ArH), 6.83 (1H, s, ArH), 7.21–7.25 (15H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 43.9, 49.5, 55.8, 55.9, 56.3, 60.7, 74.7, 82.4, 86.5, 94.8, 101.1, 106.3, 108.6, 109.4, 110.6, 119.4, 119.5, 127.0, 127.8, 128.5, 132.26, 132.28, 143.3, 147.2, 148.0, 149.1, 149.2, 176.2; EIMS *m/z* (%) 688 (M$^+$, 45), 383 (70), 244 (84), 243 (99), 195 (72), 165 (100); HREIMS *m/z* 688.2675 (calcd for $C_{42}H_{40}O_7$, 688.2661). (+)-MOM ether **12**: $[\alpha]^{20}_D$ +121 (*c* 0.67, $CHCl_3$).To an ice-cooled suspension of $LiAlH_4$ (0.36 g, 9.49 mmol) in THF (50 mL) was added a solution of MOM ether **12** (1.10 g, 1.60 mmol) in THF (10 mL). The resulting mixture was stirred at 0 °C for 30 min before addition of a saturated aqueous $MgSO_4$ solution and K_2CO_3. After stirring for 30 min, the mixture was filtered. The filtrate was concentrated to give a crude diol. To a solution of the crude diol in ether (45 mL) was added formic acid (57 mL) at 0 °C. After the solution was stirred at 0 °C for 30 min, $CHCl_3$ (100 mL) and H_2O (100 mL) were added. The organic solution was separated, washed with a saturated aqueous $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Concentration of the solvent followed by Si column chromatography (EtOAc/*n*-hexane, 2:1) gave (−)-triol **14** (0.39 g, 0.87 mmol, 54%) as a colorless oil: $[\alpha]^{20}_D$ −38 (*c* 0.78, $CHCl_3$); IR 3400, 2935, 1444, 1246, 1140, 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90−2.10 (1H, br, OH), 2.19 (1H, m, CH), 2.48 (1H, m, CH), 3.27 (1H, dd, J =

8.8, 1.3 Hz, C*H*HOH), 3.35 (1H, dd, J = 10.8, 5.3 Hz, C*H*HOH), 3.43 (3H, s, OCH_2OCH_3), 3.65 (1H, dd, J = 10.8, 2.7 Hz, CH*H*OH), 3.73 (1H, dd, J = 8.8, 7.6 Hz, CH*H*OH), 3.76–3.90 (1H, br, OH), 3.87 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.55 (2H, s, OC H_2OCH_3), 4.56 (1H, br s, OH), 4.84 (1H, d, J = 9.5 Hz, ArCHOMOM), 4.90 (1H, br d, J = 6.3 Hz, ArC*H*OH), 5.94 (1H, d, J = 3.4 Hz, OC*H*HO), 5.95 (1H, d, J = 3.4 Hz, OCH *H*O), 6.73–6.78 (3H, m, ArH), 6.85 (1H, d, J = 7.7 Hz, ArH), 6.91–6.94 (2H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 46.4, 49.5, 55.8, 55.9, 56.9, 63.0, 63.5, 73.5, 94.5, 101.1, 107.3, 108.1, 109.2, 111.0, 118.3, 121.4, 133.6, 136.6, 147.4, 147.9, 148.0, 148.9; FABMS *m/z* 451 ((M + H)$^+$, 1), 251 (78), 154 (100), 136 (73); *anal.* C 61.19%, H 6.73%, calcd for $C_{23}H_{30}O_9$, C 61.31%, H 6.72%. (+)-triol **14**: $[\alpha]^{20}_D$ +38 (*c* 0.85, $CHCl_3$). To an ice-cooled solution of the (−)-triol **14** (0.43 g, 0.95 mmol) in pyridine (7 mL) was added PivCl (0.30 mL, 2.44 mmol). The resulting mixture was stirred at room temperature for 11 h. After addition of EtOAc (100 mL) and H_2O (100 mL), the organic solution was separated, washed with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). After evaporation of the solvent, the residue was applied to Si column chromatography (EtOAc/*n*-hexane, 1:3) to give (−)-hydroxydipivaloate **16** (0.47 g, 0.76 mmol, 80%) as a colorless oil: $[\alpha]^{20}_D$ −45 (*c* 0.9, $CHCl_3$); IR 2445, 2972, 1724, 1155, 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (9H, s, *tert*-Bu), 1.18 (9H, s, *tert*-Bu), 2.44 (1H, m, CH), 2.57 (1H, m, CH), 3.48 (3H, s, OCH_2OCH_3), 3.87 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.94–4.06 (5H, m, CH_2OPiv, OH), 4.60 (2H, s, OCH_2OCH_3), 4.76 (1H, dd, J = 7.3, 4.8 Hz, ArC*H*OH), 4.83 (1H, d, J = 7.9 Hz, ArCHOMOM), 5.96 (2H, s, OCH_2O), 6.72–6.78 (3H, m, ArH), 6.83–6.86 (2H, m, ArH), 6.93 (1H, s, ArH); ^{13}C NMR ($CDCl_3$) δ 27.1, 38.7, 43.1, 44.4, 55.8, 55.9, 57.0, 64.5, 64.6, 72.3, 94.3, 101.2, 107.1, 108.2, 109.3, 111.1, 118.6, 121.1, 132.8, 136.0, 147.6, 148.2, 148.4, 149.1, 178.0, 178.1; FABMS *m/z* 619 ((M + H)$^+$, 1), 453 (62), 165 (100); *anal.* C 63.42%, H 7.61%, calcd for $C_{33}H_{46}O_{11}$, C 64.05%, H 7.50%. (+)-Hydroxy dipivaloate **16**: $[\alpha]^{20}_D$ +45 (*c* 1.6, $CHCl_3$). A mixture of (−)-hydroxydipivaloate (0.47 g, 0.76 mmol), PCC (0.23 g, 1.07 mmol), and MS 4 Å (20 mg) in CH_2Cl_2 (10 mL) was stirred at room temperature for 6 h before addition of ether. After the mixture was filtered, the filtrate was concentrated. The residue was applied to Si column chromatography (EtOAc/*n*-hexane, 1:6) to give (−)-ketone **18** (0.32 g, 0.52 mmol, 68%) as a colorless oil: $[\alpha]^{20}_D$ −77 (*c* 0.62, $CHCl_3$); IR 2974, 1724, 1670, 1481, 1246, 1155, 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (9H, s, *tert*-Bu), 1.12 (9H, s, *tert*-Bu), 2.44 (1H, m, 3-H), 3.27 (3H, s, OCH_2OCH_3), 3.94 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.11 (1H, dd, J = 11.9, 6.2 Hz, C*H*HOPiv), 4.22 (1H, m, 2-H), 4.28 (1H, dd, J = 11.9, 4.6 Hz, CH*H*OPiv), 4.33 (1H, d, J = 6.5 Hz, OC*H*HOCH$_3$), 4.40 (1H, d, J = 6.5 Hz, OCH*H*OCH$_3$), 4.37 (1H, dd, J = 10.7, 6.4 Hz, C*H*HOPiv), 4.49 (1H, dd, J = 10.7, 8.4 Hz, CH *H*OPiv), 4.66 (1H, d, J = 6.4 Hz, ArCHOMOM), 5.95 (2H, s, OCH_2O), 6.66 (1H, d, J = 7.9 Hz, ArH), 6.69 (1H, s, ArH), 6.74 (1H, d, J = 7.9 Hz, ArH), 6.90 (1H, d, J = 8.5 Hz, ArH), 7.53 (1H, d, J = 1.7 Hz, ArH), 7.64 (1H, dd, J = 8.5, 1.7 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 27.0, 27.1, 38.6, 42.6, 46.1, 56.0, 56.1, 56.3, 62.9, 64.9, 94.5, 101.1, 107.0, 108.1, 109.8, 110.5, 120.7, 123.0, 131.1, 133.5, 147.3, 148.0, 149.0, 153.3, 177.9, 178.1, 199.1; EIMS *m/z* (%) 616 (M$^+$, 0.5), 192 (100); *anal*. C 63.99%, H 7.09%, calcd for $C_{33}H_{44}O_{11}$, C 64.26%, H 7.20%. (+)-Ketone **18**: $[\alpha]^{20}_D$ +77 (*c* 0.93, $CHCl_3$).

(2*S*,3*R*)-2-(3,4-Dimethoxybenzoyl)-3-[(*R*)-(methoxymethoxy)(3,4-methylenedioxyphenyl)methyl]tetramethylene dipivaloate (19). MOM ether **13**. 100% yield; colorless oil: $[\alpha]^{20}_D$ +58 (*c* 0.2, $CHCl_3$); IR 3025, 2958, 1766, 1489, 1442, 1242, 1162, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.47 (1H, m, 3-H), 3.19 (1H, dd, J = 9.5, 2.9 Hz, C*H*HOTr), 3.35 (3H, s, OCH_2OCH_3), 3.46 (1H, dd, J = 9.5, 4.9 Hz, CH*H*OTr), 3.59 (1H, dd, J = 9.9, 3.5 Hz, 2-H), 3.64 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.54 (1H, d, J = 6.4 Hz, OC*H*HOCH$_3$), 4.56 (1H, d, J = 6.4 Hz, OCH*H*OCH$_3$), 5.14 (1H, d, J = 8.4 Hz, ArCHOMOM), 5.34 (1H, d, J = 3.5 Hz, 4-H), 5.90 (1H, s, OC*H*HO), 5.91 (1H, s, OCH*H*O), 6.23–6.25 (2H, m, ArH), 6.61 (1H, d, J = 8.7 Hz, ArH), 6.72–6.76 (2H, m, ArH), 6.78 (1H, s, ArH), 7.24–7.33 (9H, m, ArH), 7.40–7.42 (6H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 46.0, 48.8, 55.6, 55.8, 55.9, 60.3, 75.6, 81.9, 86.8, 94.2, 101.1, 107.8, 108.2, 108.5, 110.4, 119.2, 121.1, 127.1, 127.9, 128.7, 131.1, 131.3, 143.5, 147.3, 147.7, 149.07, 149.10, 175.2; EIMS *m/z* (%) 688 (M$^+$, 15), 244 (70), 243 (80), 165 (100); *anal*. C 73.52%, H 5.81%, calcd for $C_{42}H_{40}O_9$, C 73.24%, H 5.85%. Triol **15**. 66% yield (2 steps); colorless oil: $[\alpha]^{20}_D$ +109 (*c* 0.89, $CHCl_3$); IR 3400, 3010, 2937, 1249, 1027 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.78 (1H, m, CH), 1.82 (1H, br s, OH), 2.33 (1H, m, CH), 3.26 (1H, dd, J = 11.6, 5.8 Hz, C*H*HOH), 3.31 (1H, dd, J = 11.6, 3.7 Hz, CH*H*OH), 3.39 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.07 (1H, dd, J = 11.4, 3.5 Hz, C*H*HOH), 4.15 (1H, dd, J = 11.4, 5.9 Hz, CH*H*OH), 4.50 (2H, s, OCH_2OCH_3), 4.74 (1H, d, J = 9.5 Hz, ArCHOMOM), 5.07 (1H, d, J = 8.9 Hz, ArC*H*OH), 5.95 (2H, s, OCH_2O), 6.75–6.79 (4H, m, ArH), 6.88–6.91 (2H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 47.5, 48.2, 55.7, 55.9, 56.0, 60.7, 63.7, 73.6, 80.2, 94.6, 101.0, 107.8, 108.0, 109.3, 110.7, 119.0, 122.1, 134.5, 136.3, 147.2, 147.9, 148.5, 149.0; EIMS *m/z* (%) 450 (M$^+$, 6), 432 (55), 370 (98), 195 (100); HREIMS *m/z* 450.1890 (calcd for $C_{23}H_{30}O_9$, 450.1890). Hydroxydipivaloate **17**. 95% yield; colorless oil: $[\alpha]^{20}_D$ +73 (*c* 0.2, $CHCl_3$); IR 2971, 1718, 1243, 1157, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.11 (9H, s, *tert*-Bu), 1.20 (9H, s, *tert*-Bu), 2.08 (1H, m, CH), 2.43 (1H, d, J = 2.3 Hz, OH), 2.55 (1H, m, CH), 3.39 (3H, s, OCH_2OCH_3), 2.64 (1H, dd, J = 11.2, 5.4 Hz, C*H*HOPiv), 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.99 (1H, dd, J = 11.2, 8.3 Hz, OC*H*HOPiv), 4.49 (1H, d, J = 6.8 Hz, OC*H*HOCH$_3$), 4.53 (1H, d, J = 6.8 Hz, OCH *H*OCH$_3$), 4.51–4.61 (3H, m, OCH_2OPiv, ArC*H*OH), 5.09 (1H, d, J = 8.2 Hz, ArCHOMOM), 5.95 (1H, d, J = 7.8 Hz, OC*H*HO), 5.96 (1H, d, J = 7.8 Hz, OCH *H*O), 6.70 (1H, dd, J = 8.1, 1.8 Hz, ArH), 6.73 (1H, d, J = 1.8 Hz, ArH), 6.77 (1H, d, J = 8.1 Hz, ArH), 6.80 (1H, d, J = 8.3 Hz, ArH), 6.92–6.94 (2H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 27.1, 27.2, 38.6, 38.7, 43.7, 44.3, 55.6, 55.9, 56.3, 63.3, 64.5, 73.8, 78.5, 94.5, 101.0, 107.8, 108.1, 109.0, 110.9, 119.0, 122.0, 134.5, 135.6, 147.2, 147.8, 148.8, 149.3, 178.2, 178.4; FABMS *m/z* 619 ((M + H)$^+$, 0.5), 165 (100); *anal.* C 63.93%, H 7.60%, calcd for $C_{33}H_{46}O_{11}$, C 64.05%, H 7.50%. Ketone **19**. 65% yield; colorless oil: $[\alpha]^{20}_D$ +35 (*c* 0.9, $CHCl_3$); IR 2971, 1722, 1670, 1263, 1155, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03 (9H, s, *tert*-Bu), 1.13 (9H, s, *tert*-Bu), 2.55 (1H, m, 2-H), 3.40 (3H, s, OCH_2OCH_3), 3.91 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.03 (1H, m, 3-H), 4.26 (1H, dd, J = 11.8, 4.9 Hz, C*H*HOPiv), 4.41 (1H, dd, J = 11.8, 6.3 Hz, CH*H*OPiv), 4.48–4.52 (4H, m, CH_2OPiv, OCH_2OCH$_3$), 4.73 (1H, d, J = 5.4 Hz, ArCHOMOM), 5.93 (2H, s, OCH_2O), 6.62 (1H, dd, J = 8.4, 1.6 Hz, ArH), 6.69–6.71 (2H, m, ArH), 6.83 (1H, d, J = 8.4 Hz, ArH), 7.43 (1H, d, J = 2.0 Hz, ArH), 7.47 (1H, dd, J = 8.4, 2.0 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 27.0, 27.1, 38.60, 38.64, 43.4, 45.0, 55.9, 56.1, 56.4, 62.4, 64.1, 76.6, 94.6, 101.1, 107.3, 108.1, 109.8, 110.5, 121.0, 123.0, 130.5, 132.9, 147.3, 147.9, 149.1, 153.5, 178.1, 198.8; EIMS *m/z* (%) 616 (M$^+$, 0.1), 192 (100), 165 (78); HREIMS *m/z* 616.2883 (calcd for $C_{33}H_{44}O_{11}$, 616.2884).

(2*S*,3*R*,4*S*)-4-(3,4-Dimethoxybenzoyl)-2-(3,4-methylenedioxyphenyl)-3-(pivaloyloxymethyl)tetrahydrofuran [(7*S*,8*R*,8′*S*)-3′,4′-dimethoxy-3,4-methylenedioxy-7′-oxo-7,9′-epoxylignan-9-yl pivaloate] (20) and (2*R*,3*R*,4*S*)-4-(3,4-Dimethoxybenzoyl)-2-(3,4-methylenedioxyphenyl)-3-(pivaloyloxymethyl)tetrahydrofuran [(7*R*,8*R*,8′*S*)-3′,4′-dimethoxy-3,4-methylenedioxy-7′-oxo-7,9′-epoxylignan-9-yl pivaloate] (21). A solution of ketone **18** (68.0 mg, 0.11 mmol) in THF (3 mL) and 6 M aqueous HCl solution (3 mL) was stirred at room temperature for 18 h before addition of H_2O (50 mL) and EtOAc (50 mL). The organic phase was separated, washed with brine, and dried (Na_2SO_4). After evaporation of the organic solvent, the residue was applied to Si column chromatography (EtOAc/hexane, 1:5) to give tetrahydrofuran **20** (21 mg, 0.045 mmol, 41%) as a colorless oil and tetrahydrofuran **21** (8 mg, 0.017 mmol, 15%) as a colorless oil. Tetrahydrofuran **20** (40% yield) and tetrahydrofuran **21** (17% yield) were obtained from ketone **19**. Tetrahydrofuran **20**: $[\alpha]^{20}_D$ −8 (*c* 0.52, $CHCl_3$); IR 2962, 1724, 1671, 1265, 1162, 1041 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.11 (9H, s, *tert*-Bu), 3.08 (1H, m, 3-H), 3.95 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.06 (1H, m, 4-H), 4.13–4.17 (3H, m, 5-H_2, C*H*HOPiv), 4.27 (1H, dd, J = 8.7, 8.7 Hz, CH*H*OPiv), 4.62 (1H, d, J = 9.0 Hz, 2-H), 5.96 (2H, s, OCH_2O), 6.78 (1H, d, J = 8.0 Hz, ArH), 6.86 (1H, d, J = 8.0 Hz, ArH), 6.91 (1H, d, J = 8.4 Hz, ArH), 6.99 (1H, s, ArH), 7.56 (1H, s, ArH), 7.53 (1H, d, J = 8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 27.1, 38.8, 49.6, 49.8, 56.0, 56.1, 62.9, 71.1, 84.2, 101.1, 107.2, 108.1, 110.1, 110.6, 120.5, 122.9, 129.7, 133.8, 147.6, 148.0, 149.4, 153.8, 178.2, 196.6; EIMS *m/z* (%) 470 (M$^+$, 35), 203 (86), 165 (100); HREIMS *m/z* 470.1940 (calcd for $C_{26}H_{30}O_8$, 470.1940). (+)-**20**: $[\alpha]^{20}_D$ +8 (*c* 0.65, $CHCl_3$). Tetrahydrofuran **21**: $[\alpha]^{20}_D$ +88 (*c* 0.2, $CHCl_3$); IR 2927, 1724, 1670, 1508, 1263, 1151, 1041 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (9H, s, *tert*-Bu), 2.80 (1H, m, 3-H), 3.93 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.04 (1H, dd, J = 11.5, 6.7 Hz, C*H*HOPiv), 4.13 (1H, dd, J = 11.5, 7.1 Hz, CH*H*OPiv), 4.25–4.33 (2H, m, 5-H_2), 4.35 (1H, m, 4-H), 4.86 (1H, d, J = 6.7 Hz, 2-H), 5.97 (2H, s, OCH_2O), 6.79–6.90 (4H, m, ArH), 7.54–7.55 (2H, m, ArH); ^{13}C NMR ($CDCl_3$)

δ 26.9, 38.5, 46.8, 50.7, 56.0, 56.1, 62.2, 70.5, 83.7, 101.1, 106.4, 108.3, 110.0, 110.2, 119.7, 122.9, 130.4, 135.1, 147.3, 148.0, 149.4, 153.8, 178.0, 197.1; EIMS *m/z* (%) 470 (M^+, 16), 368 (95), 203 (98), 193 (98), 165 (100); HREIMS *m/z* 470.1941 (calcd for $C_{26}H_{30}O_8$, 470.1941).

(2*S*,3*R*,4*S*)-4-(3,4-Dimethoxybenzoyl)-3-hydroxymethyl-2-(3,4-methylenedioxyphenyl)tetrahydrofuran ((−)-magnolone, 1). To a solution of (−)-pivaloate **20** (15 mg, 0.032 mmol) in EtOH (1 mL) was added a 1 M aqueous NaOH solution (1 mL). The resulting solution was stirred at room temperature for 12 h before addition of EtOAc (50 mL) and H_2O (50 mL). The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration of the solvent, the residue was applied to Si column chromatography (EtOAc/*n*-hexane, 1:1) to give (−)-magnolone [(−)-**1**] (11 mg, 0.028 mmol, 88%) as a colorless oil: IR 3748, 3025, 1670, 1263, 1160, 1041 cm^{-1}; NMR data agreed with literature;[1] $[\alpha]^{20}_D$ −31 (*c* 0.2, $CHCl_3$), $[\alpha]^{20}_D$ −19 (*c* 0.4, MeOH), lit.:[1] $[\alpha]^{21}_D$ −11.25 (*c* 0.4, MeOH); EIMS *m/z* (%) 386 (M^+, 42), 165 (100); HREIMS *m/z* 386.1367 (calcd for $C_{21}H_{22}O_7$, 386.1365); more than 99% ee (HPLC, DAICEL chiral column OD-H, detected at 280 nm, 1 mL min^{-1}, 10% EtOH in hexane, t_R 48 min). (+)-Magnolone: $[\alpha]^{20}_D$ +31 (*c* 0.2, $CHCl_3$), > 99% ee (t_R 43 min).

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