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A stereoselective approach to bioactive secolignans: synthesis of peperomin C and its analogues

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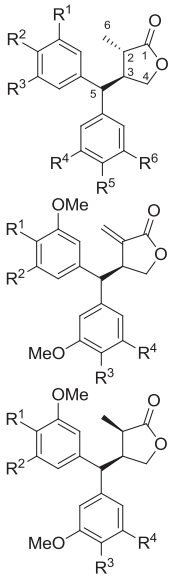
ABSTRACT

A stereoselective approach to secolignans is described. The key synthetic strategy involves an asymmetric aldol reaction to control the creation of the stereogenic center at the β-carbon of the target secolignans. In the present work, peperomin C and its analogues, i.e., 2,6-didehydropeperomin C and 2-*epi*-peperomin C were successfully synthesized in good yields with high stereoselectivities.

1. Introduction

Secolignan is a subclass of lignans[1] found in various plants that have widely been used in Chinese folk medicine. Among those, secolignans, namely peperomins A, B, C, D, and E (Fig. 1) are the well-known representatives.[2] Peperomin-type secolignans show a broad range of potent biological activities. For example, peperomins A–D, the α-methyl-γ-butyrolactone derivatives, have been found to exhibit antitumor,[2d] anti-HIV-1,[2e] and anti-angiogenic[2f] activities. Peperomin E and 2,6-didehydropeperomin B, the α-methylene-γ-butyrolactone derivatives, show inhibitory effects on the growth of cancer cell lines[2c] and anti-inflammatory activity.[2l] In addition, among a variety of peperomins, those containing an α-methylene moiety, such as peperomin E and secolignan **1**, exhibit inhibitory activity against the liver tumor cell.[2d] To date, a variety of bioactive peperomin-type secolignans, varying in the aromatic groups at C-5, the α-substituents (e.g., $-CH_2OH$, $-CH_2OR$, and $-CH_2O$-sugar), and relative orientation of the substituents at the α- and β-positions, have been reported. These include secolignans **2** and **3** bearing a rare 2,3-*cis* configuration.[3]

Due to their broad range of biological activities, peperomin-type secolignans have received considerable attention for further development as potential chemotherapeutic agents.[4] Having taken the importance of structure–activity relationship (SAR) study into account, we therefore aim toward the investigation on the development of a stereoselective methodology that would allow a practical synthesis of naturally occurring secolignans and their derivatives.[5] Herein, we wish to report our synthetic approach



	R^1	R^2	R^3	R^4	R^5	R^6
peperomin A	OMe	-OCH_2O-		OMe	-OCH_2O-	
peperomin B	OMe	OMe	OMe	OMe	-OCH_2O-	
peperomin C	OMe	OMe	OMe	OMe	OMe	OMe
peperomin D	H	-OCH_2O-		H	-OCH_2O-	

	R^1	R^2	R^3	R^4
peperomin E	-OCH_2O-		-OCH_2O-	
2,6-didehydropeperomin B	OMe	OMe	-OCH_2O-	
1	-OCH_2O-		OH	OMe

	R^1	R^2	R^3	R^4
2	-OCH_2O-		-OCH_2O-	
3	OMe	OMe	-OCH_2O-	

Fig. 1. Selected representatives of peperomin-type secolignans.

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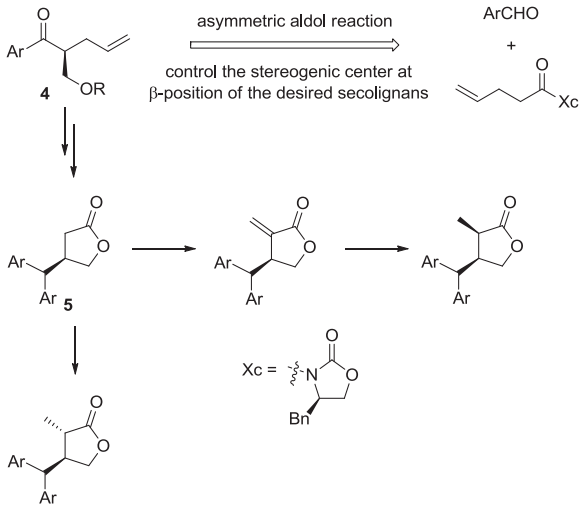
leading to the stereoselective synthesis of 2,3-*trans*, 2,3-*cis*, and α-methylene peperomin-type secolignans.

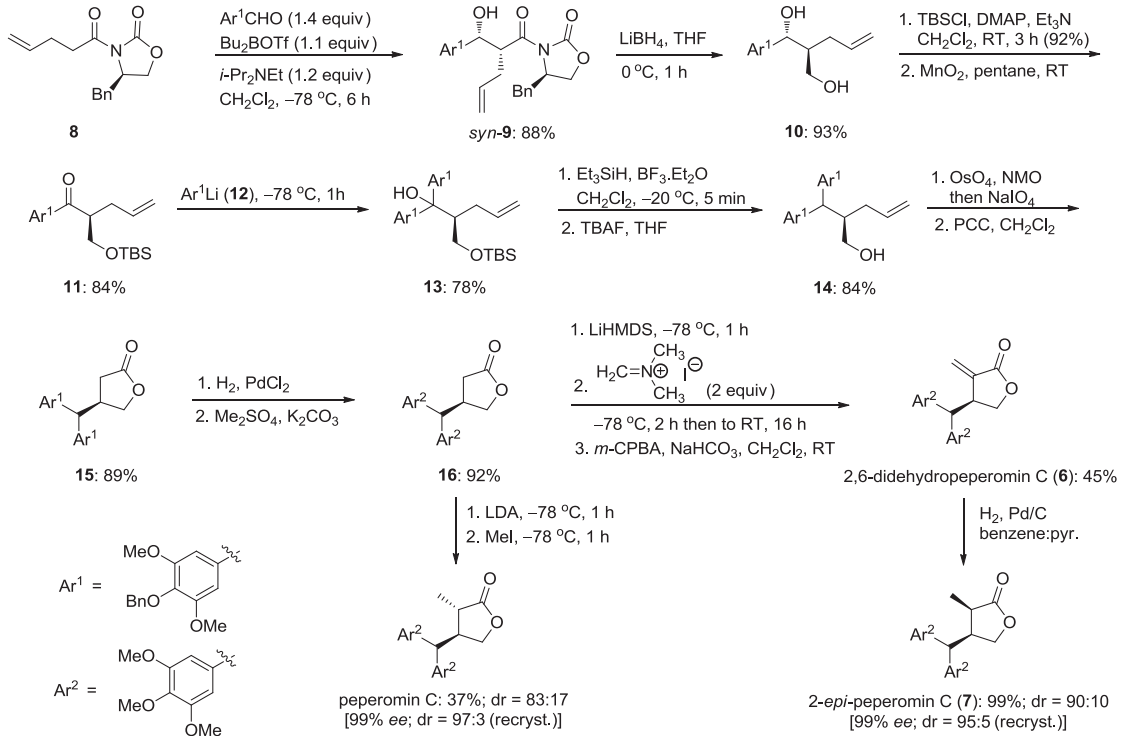
2. Results and discussion

Our synthetic approach is outlined in Scheme 1. We planned to use a chiral oxazolidinone auxiliary (Evans chiral auxiliary)[6] in an asymmetric aldol reaction as a key step to synthesize and control the creation of the stereocenter at an α-carbon of a chiral aryl ketone of type **4**. The chiral intermediate **4** can be converted into 2,3-*trans*, 2,3-*cis* as well as α-methylene secolignans *via* a chiral γ-butyrolactone **5** (Scheme 1). Here we report on stereoselective synthesis of peperomin C and its analogues, 2,6-didehydropeperomin C (**6**) and 2-*epi*-peperomin C (**7**) (Scheme 2).



Scheme 1. Synthetic plan to synthesize chiral aryl ketone **4** as a key synthetic intermediate leading to secolignans.

Our synthesis began with the synthesis of compound **8**.[7] Based on the procedure reported by Evans,[8] compound **8** was treated with 4-(benzyloxy)-3,5-dimethoxybenzaldehyde (Ar^1CHO)[9] in the presence of dibutylboron triflate (Bu_2BOTf) (1.1 equiv) and Hünig's base (*i*-Pr_2NEt) (1.2 equiv) in dry CH_2Cl_2 at −78 °C for 6 h (Scheme 2). Diastereoselective alkylation of the boron enolate derived from compound **8** with aldehyde, Ar^1CHO, proceeded with high diastereoselectivity (>99% dr, 400 MHz ^1H NMR analysis). The desired Evans' *syn* product **9**[10] was obtained in 88% yield as a single diastereomer as determined by ^1H and ^{13}C NMR analyses after chromatographic purification (see Supplementary data). Next, the conversion of the Evans' *syn* product **9** into a chiral ketone **11** was investigated. Thus, reductive cleavage of compound **9** upon treatment with $LiBH_4$[11] in THF at 0 °C for 1 h gave diol **10** (93% yield) and the recovered oxazolidinone auxiliary (87% yield). Selective protection of a primary alcohol moiety of diol **10** was achieved in high yield and selectivity by treatment of the diol **10** with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) and Et_3N in anhydrous CH_2Cl_2 at room temperature for 3 h.[12] The corresponding mono-TBS-protected alcohol was obtained in 92% yield. Subsequent benzylic oxidation using MnO_2 provided the desired chiral ketone **11** in 84% yield. Having successfully been prepared, the chiral ketone **11** was employed as a key substrate for further manipulation directed the synthesis of peperomin C and its analogues **6** and **7**. Thus, treatment of ketone **11** with [4-(benzyloxy)-3,5-dimethoxyphenyl]lithium (**12**) in THF at −78 °C for 1 h gave the corresponding diaryl alcohol **13** (78% yield). Subsequent reductive deoxygenation of the diaryl alcohol **13** was accomplished by treatment of **13** with Et_3SiH and $BF_3{\cdot}Et_2O$ in anhydrous CH_2Cl_2 at −20 °C for 5 min followed by removal of the TBS ether by using TBAF providing the required alcohol **14** (84% yield, two steps). Conversion of the alcohol **14** to chiral γ-butyrolactone **16** was achieved by a two-step reaction involving oxidative cleavage of the terminal alkene moiety of **14** followed by successive oxidation. After examining optimal conditions, it was found that treatment of **14** with OsO_4 (5 mol %), *N*-



Scheme 2. A stereoselective synthesis of peperomin C and its analogues **6** and **7**.

methylmorpholine-*N*-oxide (NMO) (3 equiv) then $NaIO_4$ (2 equiv) followed by oxidation of the resulting lactol by using pyridinium chlorochromate (PCC) in CH_2Cl_2 provided γ-butyrolactone **15** in 89% yield. Debenzylation of **15** followed by methylation of the resulting phenol product afforded γ-butyrolactone **16** in 92% yield. The synthesized γ-butyrolactone **16** shows a specific optical rotation value of $[\alpha]_D^{22}$ −13.5 (*c* 1.0, $CHCl_3$), which is consistent with that reported in the literature {$[\alpha]_D^{25}$ −13.0 (*c* 1.0, $CHCl_3$)}.[13]

For the synthesis of peperomin C, γ-butyrolactone **16** was treated with LDA (1 equiv) in THF at −78 °C followed by trapping with methyl iodide at −78 °C for 1 h. Peperomin C, together with 2-*epi*-peperomin C (**7**), was obtained in 37% yield as an 83:17 mixture of diastereomers as determined by ^1H NMR analysis. Comparable results were obtained when LiHMDS was used as a base in place of LDA. Attempts to separate peperomin C and **7** by means of chromatographic methods were unsuccessful. Fortunately, up to 97:3 diastereomeric ratio of peperomin C (15% yield) with 99% *ee* as determined by HPLC analysis (Daicel Chiral OD-H column; *i*-PrOH/hexane)[14] could be obtained after recrystallization from EtOAc/hexanes. The synthesized peperomin C shows a specific optical rotation value of $[\alpha]_D^{24}$ +27.3 (*c* 0.68, $CHCl_3$) {lit.[2a] $[\alpha]_D^{27}$ +42.7 (*c* 0.06, $CHCl_3$)}. Its ^1H and ^{13}C NMR data are in agreement with those reported for the natural compound (see Supplementary data).

Starting from γ-butyrolactone **16**, a 2,6-didehydropeperomin C (**6**) can be readily synthesized. Eschenmoser methylenation of **16** was carried out according to the previously reported procedure by Danishefsky.[15] Thus, the γ-butyrolactone **16** was treated with LiHMDS (1.5 equiv) in THF at −78 °C for 1 h followed by trapping with the Eschenmoser salt (2 equiv) and the resulting was maintained at −78 °C (2 h) and at room temperature (16 h). Without purification, the corresponding adduct was subsequently treated with *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of $NaHCO_3$. The desired 2,6-didehydropeperomin C (**6**) was obtained in 45% yield after chromatographic purification.

Finally, the conversion of 2,6-didehydropeperomin C (**6**) into 2-*epi*-peperomin C (**7**) should be straightforward through a simple catalytic hydrogenation. It is expected that the bulkiness of the β-diarylmethyl group of **6** would direct the hydrogenation process to take place from the opposite site in order to avoid the steric interaction leading to 2-*epi*-peperomin C (**7**) with a 2,3-*cis* stereochemistry as a major diastereomer. Therefore, catalytic hydrogenation of **6** (H_2, Pd/C, EtOH)[16] provided **7** in 91% yield with good diastereoselectivity (dr=90:10) as determined by ^1H NMR analysis. Similar results were obtained when pyridine was used as a co-solvent for hydrogenation (H_2, Pd/C) in dry benzene;[17] **7** was obtained in 99% yield (dr=90:10). Compound **7** (12% yield; 99% *ee*) with the diastereomeric ratio up to 95:5 as determined by HPLC analysis (Daicel Chiral OD-H column; *i*-PrOH/hexane)[14] could be obtained after recrystallization from EtOAc/hexanes. The 2,3-*cis* stereochemistry of **7** was confirmed from NOE experiments as depicted in Fig. 2 (see Supplementary data). Irradiation of H-3 resulted in an NOE enhancement for H-2. Additionally, upon irradiation of $-CH_3$-6, an NOE enhancement was observed for H-5.

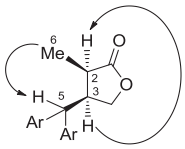


Fig. 2. The key NOE correlations of 2-*epi*-peperomin C (**7**).

3. Conclusions

In conclusion, we have reported a stereoselective approach to synthesize peperomin-type secolignans. Based on this approach, secolignans containing two symmetrical aromatic rings at C-5, such as peperomin C, were obtained in high stereoselectivity. Moreover, its analogues bearing an α-methylene moiety and 2,3-*cis* stereochemistry, i.e., 2,6-didehydropeperomin C and 2-*epi*-peperomin C, respectively, were also readily synthesized in good yields and stereoselectivities. The present approach should be found useful for the SAR study of peperomin-type secolignans since naturally occurring secolignans and their derivatives, varying in the α-substituents and the relative orientation of the α- and β-substituents of γ-butyrolactone ring, could be readily prepared according to our reported methodology.

4. Experimental section

4.1. General

The ^1H NMR spectra were recorded on a Bruker DPX-300 (300 MHz) or a Bruker-400 (400 MHz) spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker DPX-300 (75 MHz) or a Bruker-400 (100 MHz) spectrometer in $CDCl_3$. The chemical shifts are reported as δ-values in parts per million (ppm) relative to the deuterated solvent peak; $CDCl_3$ (δ_H: 7.27, δ_C: 77.0) or TMS (δ_H: 0.00). The IR spectra were recorded on a Perkin Elmer Spectrum GX FT-IR spectrometer. The mass spectra were recorded by using a Thermo Finnigan Polaris Q mass spectrometer. The high-resolution mass spectra were recorded on an HR-TOF-MS Micromass model VQ-TOF2 mass spectrometer. Melting points were recorded on a Buchi M-565 melting Point Apparatus and uncorrected. HPLC was performed with Agilent 1100 Series HPLC Value System using *i*-PrOH/hexanes as mobile phase. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl. Dichloromethane (CH_2Cl_2) and pentane were distilled over calcium hydride and stored over activated molecular sieves (4 Å). Methanol (MeOH) was distilled over Mg powder. Column chromatography was performed by using Merck silica gel 60 (Art 7734). Other common solvents [CH_2Cl_2, hexanes, ethyl acetate (EtOAc), MeOH, and acetone] were distilled before use.

4.2. (*R*)-4-Benzyl-3-(pent-4-enoyl)oxazolidin-2-one (8)

Compound (**8**) was synthesized according to the literature procedure[7] and obtained (492 mg, 95% yield) as a colorless liquid; R_f (20% EtOAc/hexanes) 0.33; $[\alpha]_D^{23}$ −61.7 (*c* 0.8, $CHCl_3$) {lit.[7d] $[\alpha]_D^{23}$ −55 (*c* 0.8, $CHCl_3$)}; IR (neat): ν_{max} 1777, 1702, 1384, 1211, 916 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H, Ar*H*), 5.90 (ddt, *J*=17.1, 10.3, 6.6 Hz, 1H, C*H*), 5.13 (dd, *J*=17.1, 1.4 Hz, 1H, C*H*H), 5.06 (dd, *J*=10.3, 1.1 Hz, 1H, CH*H*), 4.77–4.64 (m, 1H, C*H*), 4.27–4.17 (m, 2H, CH_2O), 3.32 (dd, *J*=13.4, 3.1 Hz, 1H, C*H*H), 3.20–2.96 (m, 2H, CH_2), 2.79 (dd, *J*=13.4, 9.6 Hz, 1H, CH*H*), 2.55–2.42 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5 (CO), 153.4 (CO), 136.6 (CH), 135.2 (C), 129.4 (2×CH), 128.9 (2×CH), 127.3 (CH), 115.7 (CH_2), 66.1 (CH_2), 55.1 (CH), 37.8 (CH_2), 34.7 (CH_2), 28.1 (CH_2); *m*/*z* (EI) 260 [$(M+H)^+$, 25], 259 (M^+, 100), 231 (17), 178 (28), 117 (29), 91 (44), 55 (50); HRMS (ESI-TOF): MNa^+, found 282.1101. $C_{15}H_{17}NO_3Na$ requires 282.1106.

4.3. (*R*)-4-Benzyl-3-{(*R*)-2-{(*R*)-[4-(benzyloxy)-3,5-dimethoxyphenyl](hydroxy)methyl}pent-4-enoyl}oxazolidin-2-one (9)

To a solution of compound **8** (457 mg, 1.76 mmol) in dry CH_2Cl_2 (4.5 mL) cooled at −78 °C was added a solution of Bu_2BOTf (1 M in CH_2Cl_2, 1.94 mL, 1.94 mmol) dropwise over 10 min. The resulting solution was allowed to stir at −78 °C for 30 min, and then *i*-Pr_2NEt (0.36 mL, 2.6 mmol) was slowly added. After stirring at −78 °C for 45 min, a solution of 4-(benzyloxy)-3,5-dimethoxybenzaldehyde

(528 mg, 1.94 mmol) in dry CH_2Cl_2 (1.7 mL) was added dropwise over 10 min, then the resulting reaction mixture was allowed to stir at −78 °C for 6 h and quenched with phosphate buffer (pH 7, 4 mL) at −78 °C. The cooling bath was replaced by an ice-bath then MeOH (6 mL) was added followed by the addition of a solution mixture of MeOH and 30% aqueous H_2O_2 solution [2:1 (v/v), 6 mL]. After stirring at 0 °C for 1 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL), and then the solvents were removed in vacuo. The resulting residue was dissolved in EtOAc and H_2O and extracted with EtOAc (3×30 mL). The combined organic phase was washed with a saturated aqueous $NaHCO_3$ solution, brine, and dried over anhydrous Na_2SO_4. Purification by column chromatography [SiO_2, 20% EtOAc/hexanes] gave *syn*-aldol product **9** (820 mg, 88% yield) as a pale yellow viscous oil; R_f (40% EtOAc/hexanes) 0.31; $[\alpha]_D^{22}$ −69.9 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3528, 1778, 1690, 1594, 1500, 1463, 1385, 1130 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49–7.44 (m, 2H, Ar*H*), 7.34–7.23 (m, 6H, Ar*H*), 7.19–7.14 (m, 2H, Ar*H*), 6.62 (s, 2H, Ar*H*), 5.95–5.80 (m, 1H, C*H*), 5.12 (dd, *J*=17.1, 1.2 Hz, 1H, C*H*H), 5.05 (d, *J*=10.1 Hz, 1H, CH*H*), 4.98 (s, 2H, CH_2O), 4.88 (d, *J*=6.2 Hz, 1H, C*H*), 4.51 (ddd, *J*=10.1, 6.2, 4.1 Hz, 1H, C*H*), 4.39–4.32 (m, 1H, C*H*), 3.99 (dd, *J*=9.0, 2.4 Hz, 1H, C*H*H), 3.82 (s, 6H, 2×OCH_3), 3.79 (dd, *J*=8.5, 8.5 Hz, 1H, CH*H*), 3.19 (dd, *J*=13.4, 3.2 Hz, 1H, C*H*H), 2.73–2.53 (m, 4H, CH*H*, CH_2 and O*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4 (CO), 153.4 (2×C), 153.1 (CO), 137.7 (C), 137.0 (C), 136.2 (C), 135.2 (CH), 135.1 (C), 129.3 (2×CH), 128.9 (2×CH), 128.4 (2×CH), 128.1 (2×CH), 127.8 (CH), 127.4 (CH), 117.3 (CH_2), 103.2 (2×CH), 75.0 (CH), 74.9 (CH_2), 65.9 (CH_2), 56.1 (2×CH_3), 55.6 (CH), 49.3 (CH), 38.0 (CH_2), 32.4 (CH_2); *m*/*z* (EI) 531 (M^+, 13), 336 (23), 263 (27), 181 (23), 91 (100); HRMS (ESI-TOF): MNa^+, found 554.2147. $C_{31}H_{33}NO_7Na$ requires 554.2155.

4.4. (1*R*,2*S*)-2-Allyl-1-[4-(benzyloxy)-3,5-dimethoxyphenyl] propane-1,3-diol (10)

To a solution of *syn*-aldol adduct **9** (539 mg, 1.0 mmol) in dry THF (3 mL) cooled at 0 °C were added dry MeOH (90 μL, 2.2 mmol) and a solution of $LiBH_4$ (51 mg, 2.3 mmol) in dry THF (3.5 mL) under an argon atmosphere. The reaction mixture was stirred at 0 °C for 1 h, then quenched with an aqueous NaOH solution (1 M, 3 mL) and extracted with EtOAc (3×30 mL). The combined organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification by column chromatography [SiO_2, 100% Et_2O] gave the diol **10** (336 mg, 93% yield) as a colorless liquid; R_f (100% Et_2O) 0.25; $[\alpha]_D^{22}$ +15.0 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3407, 1639, 1592, 1504, 1456, 1419, 1328, 1234, 1127, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J*=6.7 Hz, 2H, Ar*H*), 7.29–7.17 (m, 3H, Ar*H*), 6.46 (s, 2H, Ar*H*), 5.66 (ddt, *J*=17.0, 10.0, 7.1 Hz, 1H, C*H*), 5.00–4.89 (m, 2H, C*HH*), 4.92 (s, 2H, CH_2O), 4.81 (d, *J*=4.1 Hz, 1H, C*H*), 3.72 (s, 6H, 2×OCH_3), 3.65–3.52 (m, 2H, CH_2), 2.08–1.95 (m, 2H, CH_2), 1.90–1.81 (m, 1H, C*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2 (2×C), 138.3 (C), 137.7 (C), 137.0 (CH), 135.7 (C), 128.4 (2×CH), 128.0 (2×CH), 127.8 (CH), 116.4 (CH_2), 103.1 (2×CH), 76.1 (CH), 74.9 (CH_2), 63.7 (CH_2), 56.0 (2×CH_3), 46.2 (CH), 29.8 (CH_2); *m*/*z* (EI) 358 (M^+, 36), 341 (20), 273 (19), 267 (29), 249 (34), 156 (100), 124 (17), 91 (40); HRMS (ESI-TOF): MNa^+, found 381.1678. $C_{21}H_{26}O_5Na$ requires 381.1678.

4.5. (*S*)-1-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-2-{[(*tert*-butyldimethylsilyl)oxy]methyl}pent-4-en-1-one (11)

To a mixture of diol **10** (307 mg, 0.85 mmol) and DMAP (10 mg, 0.085 mmol) in dry CH_2Cl_2 (3 mL), Et_3N (0.36 mL, 2.55 mmol) was added. The resulting reaction mixture was then treated with a solution of TBSCl (384 mg, 2.55 mmol) in dry CH_2Cl_2 (3 mL) at room temperature. The progress of the reaction was monitored by TLC. After the complete consumption of the starting material (3 h), the reaction mixture was quenched with H_2O (5 mL) and extracted with EtOAc (3×30 mL). The combined organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification by column chromatography [SiO_2, 20% EtOAc/hexanes] gave the corresponding mono-TBS protected alcohol (370 mg, 92% yield) as a colorless liquid; R_f (20% EtOAc/hexanes) 0.40; $[\alpha]_D^{22}$ +14.4 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3486, 1592, 1504, 1463, 1328, 1252, 1232, 1130, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J*=7.1 Hz, 2H, Ar*H*), 7.27–7.16 (m, 3H, Ar*H*), 6.48 (s, 2H, Ar*H*), 5.66–5.54 (m, 1H, C*H*), 4.97–4.90 (m, 2H, C*HH*), 4.92 (s, 2H, CH_2O), 4.90–4.86 (m, 1H, C*H*), 3.73 (s, 6H, 2×OCH_3), 3.70 (d, *J*=2.6 Hz, 1H, O*H*), 3.67 (d, *J*=4.0 Hz, 2H, CH_2), 2.14–1.94 (m, 2H, CH_2), 1.83–1.75 (m, 1H, C*H*), 0.85 [s, 9H, Si(CH_3)$_3$], 0.01 (s, 3H, SiCH_3), 0.00 (s, 3H, SiCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2 (2×C), 138.6 (C), 137.9 (C), 137.1 (CH), 135.6 (C), 128.5 (2×CH), 128.0 (2×CH), 127.7 (CH), 116.4 (CH_2), 103.1 (2×CH), 76.6 (CH), 74.9 (CH_2), 64.5 (CH_2), 56.1 (2×CH_3), 46.2 (CH), 29.0 (CH_2), 25.8 (3×CH_3), 18.1 (C), −5.5 (CH_3), −5.6 (CH_3); *m*/*z* (EI) 472 (M^+, 46), 367 (100), 323 (24), 231 (30), 211 (94), 91 (51); HRMS (ESI-TOF): MNa^+, found 495.2535. $C_{27}H_{40}O_5SiNa$ requires 495.2543.

To a solution of mono-TBS protected alcohol (1.73 g, 3.66 mmol) in dry *n*-pentane (40 mL) was added MnO_2 (9.56 g, 110 mmol) at room temperature. The resulting brown suspension was stirred at room temperature, and the progress of the reaction was monitored by TLC. After the complete consumption of the starting material (12 h), the reaction mixture was filtered through Celite pad, and the residue was eluted with EtOAc (250 mL). Compound **11** (1.44 g, 84% yield) was obtained as a yellow oil; R_f (20% EtOAc/hexanes) 0.52; $[\alpha]_D^{22}$ +2.3 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 1674, 1584, 1502, 1463, 1415, 1323, 1129, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50–7.45 (m, 2H, Ar*H*), 7.37–7.26 (m, 3H, Ar*H*), 7.22 (s, 2H, Ar*H*), 5.75 (ddt, *J*=17.1, 10.1, 7.0 Hz, 1H, C*H*), 5.15 (s, 2H, CH_2O), 5.05 (dd, *J*=17.1, 1.5 Hz, 1H, C*H*H), 4.99 (d, *J*=10.1 Hz, 1H, CH*H*), 3.92–3.84 (m, 1H, C*H*H), 3.88 (s, 6H, 2×OCH_3), 3.79–3.66 (m, 2H, CH*H* and C*H*), 2.48 (ddd, *J*=14.1, 7.0, 7.0 Hz, 1H, C*H*H), 2.31 (ddd, *J*=14.1, 7.0, 7.0 Hz, 1H, CH*H*), 0.8 [s, 9H, SiC(CH_3)$_3$], 0.0 (s, 3H, SiCH_3), −0.6 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8 (CO), 153.2 (2×C), 141.3 (C), 137.4 (C), 135.4 (CH), 133.4 (C), 128.4 (2×CH), 128.1 (2×CH), 127.9 (CH), 116.8 (CH_2), 106.0 (2×CH), 74.9 (CH_2), 64.9 (CH_2), 56.2 (2×CH_3), 48.6 (CH), 33.4 (CH_2), 25.7 (3×CH_3), 18.1 (C), −5.6 (2×CH_3); *m*/*z* (EI) 471 [(M+H)$^+$, 3], 413 (100), 281 (17), 91 (17). HRMS (ESI-TOF): MNa^+, found 493.2381. $C_{27}H_{38}O_5SiNa$ requires 493.2386.

4.6. (*S*)-1,1-Bis[4-(benzyloxy)-3,5-dimethoxyphenyl]-2-{[(*tert*-butyldimethylsilyl)oxy]methyl}pent-4-en-1-ol (13)

A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with 2-(benzyloxy)-5-bromo-1,3-dimethoxybenzene (142 mg, 0.44 mmol) and dry THF (0.5 mL). The solution was cooled to −78 °C, and then a solution of *n*-BuLi (1.85 M in hexanes, 0.24 mL, 0.44 mmol) was added dropwise, and the stirring was continued for 10 min to provide aryllithium **12**. A solution of compound **11** (106 mg, 0.23 mmol) in dry THF (0.5 mL) was then added dropwise. The resulting yellow solution was allowed to stir at −78 °C for 1 h, then quenched with a saturated aqueous NH_4Cl solution (5 mL) and extracted with EtOAc (3×30 mL). The combined organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography [SiO_2, 20% EtOAc/hexanes] gave **13** (125 mg, 78% yield) as a yellow oil; R_f (20% EtOAc/hexanes) 0.31; $[\alpha]_D^{23}$ −22.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3420, 1591, 1505, 1464, 1416, 1321, 1132, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52–7.45 (m, 4H, Ar*H*), 7.37–7.25 (m, 6H, Ar*H*), 6.81 (s, 2H, Ar*H*), 6.80 (s, 2H, Ar*H*), 5.88–5.77 (m, 1H, C*H*), 5.22 (s, 1H, O*H*), 5.08 (brs, 1H, C*H*H), 5.05 (d, *J*=3.6 Hz, 1H, CH*H*), 5.00 (s, 2H, CH_2O), 4.99 (s, 2H, CH_2O), 3.83 (s, 6H, 2×OCH_3), 3.82 (s, 6H,

2×OCH_3), 3.77 (dd, J=10.0, 2.0 Hz, 1H, CHH), 3.67 (d, J=10.0 Hz, 1H, CHH), 2.56–2.44 (m, 1H, CHH), 2.39 (dd, J=10.0, 1.3 Hz, 1H, CH), 2.24 (dd, J=13.9, 5.7 Hz, 1H, CHH), 0.91 [s, 9H, SiC(CH_3)$_3$], 0.01 (s, 3H, SiCH_3), −0.05 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1 (2×C), 153.0 (2×C), 143.5 (C), 141.7 (C), 137.9 (C), 137.8 (C), 137.2 (CH), 135.5 (C), 135.4 (C), 128.3 (4×CH), 128.0 (4×CH), 127.7 (CH), 127.6 (CH), 116.4 (CH_2), 102.9 (2×CH), 102.8 (2×CH), 81.3 (C), 74.9 (CH_2), 74.8 (CH_2), 62.1 (CH_2), 56.2 (2×CH_3), 56.1 (2×CH_3), 46.1 (CH), 30.0 (CH_2), 25.7 (3×CH_3), 18.0 (C), −5.95 (CH_3), −5.99 (CH_3); m/z (EI) 714 (M^+, 1), 551 (14), 515 (46), 473 (51), 461 (100), 370 (33), 91 (45); HRMS (ESI-TOF): MNa^+, found 737.3482. $C_{42}H_{54}O_8SiNa$ requires 737.3486.

4.7. (*R*)-2-{Bis[4-(benzyloxy)-3,5-dimethoxyphenyl]methyl} pent-4-en-1-ol (14)

To a solution of **13** (788 mg, 1.1 mmol) in dry CH_2Cl_2 (18 mL) cooled at −20 °C under an argon atmosphere was added Et_3SiH (0.88 mL, 5.5 mmol) followed by the addition of $BF_3{\cdot}OEt_2$ (0.4 mL, 3.3 mmol). After the complete consumption of the starting material (5 min), the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography [SiO_2, 20% EtOAc/hexanes] gave the corresponding product (696 mg, 91% yield) as a yellow oil; R_f (20% EtOAc/hexanes) 0.40; $[\alpha]_D^{24}$ −14.1 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 1589, 1506, 1456, 1417, 1326, 1241, 1130, 836 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.49–7.44 (m, 4H, ArH), 7.30–7.24 (m, 6H, ArH), 6.52 (s, 2H, ArH), 6.50 (s, 2H, ArH), 5.78 (ddt, J=17.2, 10.0, 7.1 Hz, 1H, CH), 5.03–4.90 (m, 6H, CHH and 2×CH_2), 3.82 (s, 6H, 2×OCH_3), 3.80 (s, 6H, 2×OCH_3), 3.73 (d, J=10.9 Hz, 1H, CH), 3.53 (dd, J=9.8, 2.8 Hz, 1H, CHH), 3.33 (dd, J=9.8, 4.0 Hz, 1H, CHH), 2.25–2.15 (m, 1H, CH), 2.15–2.02 (m, 2H, CH_2), 0.9 [s, 9H, Si(CH_3)$_3$], −0.05 (s, 3H, SiCH_3), −0.08 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.4 (2×C), 153.3 (2×C), 139.7 (C), 139.5 (C), 137.9 (2×C), 137.0 (CH), 135.6 (C), 135.5 (C), 128.4 (4×CH), 128.1 (4×CH), 127.7 (2×CH), 116.2 (CH_2), 105.6 (2×CH), 105.4 (2×CH), 75.0 (CH_2), 74.9 (CH_2), 61.2 (CH_2), 56.3 (2×CH_3), 56.2 (2×CH_3), 53.3 (CH), 44.5 (CH), 33.0 (CH_2), 25.9 (3×CH_3), 18.3 (C), −5.5 (CH_3), −5.6 (CH_3); m/z (EI) 698 (M^+, 11), 641 (9), 475 (100), 433 (49), 421 (31), 384 (44), 91 (40); HRMS (ESI-TOF): MNa^+, found 721.3537. $C_{42}H_{54}O_7SiNa$ requires 721.3537.

To a solution of the above-mentioned compound (346 mg, 0.5 mmol) in dry THF (1 mL) cooled at 0 °C was added dropwise a solution of TBAF (1 M in THF, 2.6 mL, 2.6 mmol). The reaction mixture was stirred and slowly warmed up to room temperature overnight. The reaction mixture was quenched with H_2O (15 mL) and extracted with EtOAc (3×30 mL). The combined organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography [SiO_2, 40% EtOAc/hexanes] gave **14** (269 mg, 92% yield) as a yellow oil; R_f (40% EtOAc/hexanes) 0.38; $[\alpha]_D^{22}$ −27.2 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3522, 1590, 1506, 1456, 1418, 1326, 1241, 1128, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (brd, J=7.5 Hz, 4H, ArH), 7.36–7.23 (m, 6H, ArH), 6.52 (s, 4H, ArH), 5.90–5.77 (m, 1H, CH), 5.05 (s, 1H, CHH), 5.01 (d, J=8.6 Hz, 1H, CHH), 4.98 (s, 2H, CH_2), 4.96 (s, 2H, CH_2), 3.80 (s, 6H, 2×OCH_3), 3.79 (s, 6H, 2×OCH_3), 3.72 (d, J=11.2 Hz, 1H, CH), 3.61 (dd, J=11.0, 3.6 Hz, 1H, CHH), 3.48 (dd, J=11.0, 4.6 Hz, 1H, CHH), 2.38–2.27 (m, 1H, CH), 2.22–2.12 (m, 1H, CHH), 2.11–2.01 (m, 1H, CHH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5 (2×C), 153.4 (2×C), 139.1 (C), 139.0 (C), 137.8 (2×C), 136.7 (CH), 135.6 (C), 135.5 (C), 128.3 (4×CH), 128.0 (4×CH), 127.7 (2×CH), 116.6 (CH_2), 105.4 (2×CH), 105.1 (2×CH), 74.9 (2×CH_2), 62.6 (CH_2), 56.2 (2×CH_3), 56.1 (2×CH_3), 53.7 (CH), 44.3 (CH), 33.9 (CH_2); m/z (EI) 584 (M^+, 20), 493 (49), 475 (19), 402 (19), 334 (33), 317 (28), 285 (13), 243 (18), 91 (100); HRMS (ESI-TOF): MNa^+, found 607.2668. $C_{36}H_{40}O_7Na$ requires 607.2672.

4.8. (3*R*)-3-{Bis[4′-(benzyloxy)-3′,5′-dimethoxyphenyl] methyl}butyrolactone (15)

To a solution mixture of **14** (190 mg, 0.32 mmol) and NMO (113 mg, 0.96 mmol) in CH_2Cl_2 (13 mL) were added a solution of OsO_4 (2.5% in *t*-BuOH, 0.16 mL, 0.016 mmol) and H_2O (0.16 mL, 8.9 mmol) consecutively at room temperature. The resulting yellow solution was stirred at room temperature, and the progress of the reaction was monitored by TLC. After the complete consumption of the starting material (9 h), $NaIO_4$ (137 mg, 0.64 mmol) was added to the reaction mixture at room temperature. After stirring for 30 min, the reaction mixture was quenched with a saturated aqueous $Na_2S_2O_3$ solution (15 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent, the obtained crude product was dissolved in dry CH_2Cl_2 (13 mL), and PCC (104 mg, 0.48 mmol) was added at room temperature. After stirring for 4 h, the reaction mixture was diluted and extracted with EtOAc (3×30 mL). The combined organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography [SiO_2, 50% EtOAc/hexanes] gave **15** (167 mg, 89% yield) as a pale yellow oil; R_f (50% EtOAc/hexanes) 0.38; $[\alpha]_D^{22}$ −6.4 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max} 1774, 1591, 1505, 1463, 1133 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J=7.1 Hz, 4H, ArH), 7.37–7.24 (m, 6H, ArH), 6.44 (s, 4H, ArH), 4.98 (s, 4H, 2×CH_2), 4.26 (dd, J=9.4, 7.2 Hz, 1H, CHH), 3.99 (dd, J=9.4, 6.8 Hz, 1H, CHH), 3.81 (s, 12H, 4×OCH_3), 3.65 (d, J=11.6 Hz, 1H, CH), 3.36–3.23 (m, 1H, CH), 2.58 (dd, J=17.8, 8.3 Hz, 1H, CHH), 2.29 (dd, J=17.8, 7.7 Hz, 1H, CHH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5 (CO), 153.8 (2×C), 153.7 (2×C), 137.7 (2×C), 137.3 (2×C), 136.2 (C), 136.1 (C), 128.4 (4×CH), 128.1 (4×CH), 127.8 (2×CH), 104.9 (2×CH), 104.8 (2×CH), 74.9 (2×CH_2), 72.0 (CH_2), 56.3 (4×CH_3), 55.6 (CH), 40.3 (CH), 34.1 (CH_2); m/z (EI) 584 (M^+, 23), 493 (100), 461 (31), 403 (17), 371 (29), 334 (26), 317 (77), 181 (20), 91 (98); HRMS (ESI-TOF): MNa^+, found 607.2301. $C_{35}H_{36}O_8Na$ requires 607.2308.

4.9. (3*R*)-3-[Bis(3′,4′,5′-trimethoxyphenyl)methyl]butyrolactone (16)[5b]

Compound **15** (175 mg, 0.3 mmol) and $PdCl_2$ (106 mg, 0.6 mmol) were dissolved in dry MeOH (6 mL) under an argon atmosphere. The argon inlet was replaced by a hydrogen gas balloon, and the reaction mixture was stirred at room temperature. After the complete consumption of the starting material (2 h), the reaction mixture was filtered through Celite pad, and the residue was then washed with EtOAc (150 mL). After removal of the solvent, the obtained crude product was dissolved in acetone (0.25 mL) then $(MeO)_2SO_2$ (0.11 mL, 1.2 mmol) and anhydrous K_2CO_3 (124 mg, 0.9 mmol) were added. The reaction mixture was heated to reflux for 1 h then it was cooled to room temperature and extracted with EtOAc (3×30 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography [SiO_2, 50% EtOAc/hexanes] gave a white solid of **16** in 92% yield (119 mg); R_f (50% EtOAc/hexanes) 0.13; $[\alpha]_D^{22}$ −13.5 (*c* 1.0, $CHCl_3$); mp 168–170 °C (EtOAc/hexanes) [lit.[5b] $[\alpha]_D^{25}$ −13.0 (*c* 1.0, $CHCl_3$); mp 168–169 °C]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.47 (d, J=1.2 Hz, 4H, ArH), 4.30 (dd, J=9.5, 7.2 Hz, 1H, CHH), 4.00 (dd, J=9.5, 6.6 Hz, 1H, CHH), 3.86 (s, 12H, 4×OCH_3), 3.82 (s, 6H, 2×OCH_3), 3.66 (d, J=11.7 Hz, 1H, CH), 3.38–3.28 (m, 1H, CH), 2.61 (dd, J=17.8, 8.3 Hz, 1H, CHH), 2.30 (dd, J=17.8, 7.5 Hz, 1H, CHH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4 (CO), 153.6 (2×C), 153.5 (2×C), 137.6 (2×C), 137.2 (2×C), 104.7 (2×CH), 104.6 (2×CH), 72.0 (CH_2), 60.8 (2×CH_3), 56.2 (4×CH_3), 55.7 (CH),

40.2 (CH), 34.0 (CH_2). ^1H and ^{13}C NMR data of **16** are identical with those reported in the literature.

4.10. Peperomin C

To a solution of *i*-Pr_2NH (50 μL, 0.33 mmol) in dry THF (0.5 mL) cooled at −78 °C under an argon atmosphere was added dropwise *n*-BuLi (1.71 M in hexanes, 0.16 mL, 0.27 mmol). After stirring at −78 °C for 30 min, a solution of **16** (133 mg, 0.3 mmol) in dry THF (0.5 mL) was added dropwise, then the resulting reaction mixture was allowed to stir at −78 °C for 1 h. MeI (20 μL, 0.33 mmol) was then added to the reaction mixture at −78 °C and the stirring was continued for 1 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc (3×30 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography [SiO_2, 50% EtOAc/hexanes] to provide peperomin C as a white solid (50 mg, 37% yield, 83:17 dr). Recrystallization from EtOAc/hexanes gave peperomin C with 99% *ee* and 97:3 dr; R_f (50% EtOAc/hexanes) 0.16; $[\alpha]_D^{24}$ +27.3 (*c* 0.68, $CHCl_3$) {lit.[5b] $[\alpha]_D^{25}$ +43.3 (*c* 0.06, $CHCl_3$), lit.[2a] $[\alpha]_D^{27}$ +42.7 (*c* 0.06, $CHCl_3$)}; mp 149–150 °C (EtOAc/hexanes) [lit.[2a] mp 158–160 °C (MeOH)]; ^1H NMR (400 MHz, $CDCl_3$): δ 6.49 (s, 2H, Ar*H*), 6.48 (s, 2H, Ar*H*), 4.31 (dd, *J*=9.6, 7.6 Hz, 1H, C*H*H), 3.86 (s, 6H, 2×OCH_3), 3.85 (s, 6H, 2×OCH_3), 3.86–3.83 (m, 1H, C*H*H), 3.82 (s, 6H, 2×OCH_3), 3.65 (d, *J*=11.4 Hz, 1H, C*H*), 2.99–2.88 (m, 1H, C*H*), 2.43–2.33 (m, 1H, C*H*), 0.94 (d, *J*=7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.8 (CO), 153.6 (2×C), 153.5 (2×C), 137.5 (2×C), 137.1 (2×C), 104.8 (2×CH), 104.7 (2×CH), 70.4 (CH_2), 60.9 (CH_3), 60.8 (CH_3), 56.6 (CH), 56.3 (4×CH_3), 47.4 (CH), 40.3 (CH), 15.8 (CH_3).

4.11. 2,6-Didehydropeperomin C (6)

To a solution of hexamethyldisilazane (0.1 mL, 0.48 mmol) in dry THF (0.5 mL) cooled at −78 °C under an argon atmosphere was added dropwise *n*-BuLi (1.71 M in hexanes, 0.23 mL, 0.4 mmol). After stirring at −78 °C for 30 min, a solution of **16** (97 mg, 0.22 mmol) in dry THF (0.5 mL) was added dropwise, then the resulting reaction mixture was allowed to stir at −78 °C for 1 h. Eschenmoser's salt (122 mg, 0.66 mmol) was then added to the reaction mixture at −78 °C. After stirring at −78 °C for 30 min, the reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The reaction mixture was diluted with Et_2O (10 mL) then quenched with a saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After removal of solvent, the crude mixture was dissolved in CH_2Cl_2 (3 mL), and a saturated aqueous $NaHCO_3$ solution (1.4 mL) and *m*-CPBA (76 mg, 0.44 mmol) were added. The reaction mixture was stirred at room temperature for 1 h then extracted with CH_2Cl_2 (3×30 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography [SiO_2, 50% EtOAc/hexanes] gave **6** (44 mg, 45% yield) as a white solid; R_f (50% EtOAc/hexanes) 0.28; $[\alpha]_D^{25}$ −7.8 (*c* 0.77, $CHCl_3$); mp 166–167 °C (EtOAc/hexanes); IR ($CHCl_3$): ν_{max} 1761, 1592, 1506, 1464, 1421, 1329, 1242, 1132, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=6.49 (s, 2H, Ar*H*), 6.48 (s, 2H, Ar*H*), 6.16 (d, *J*=2.1 Hz, 1H, CH*H*), 4.87 (d, *J*=2.1 Hz, 1H, CH*H*), 4.34 (dd, *J*=9.6, 7.7 Hz, 1H, CH*H*), 4.03 (dd, *J*=9.6, 4.4 Hz, 1H, C*H*H), 3.86 (s, 6H, 2×OCH_3), 3.85 (s, 6H, 2×OCH_3), 3.83 (s, 6H, 2×OCH_3), 3.90–3.80 (m, 1H, C*H*), 3.74 (d, *J*=11.5 Hz, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.8 (CO), 153.6 (2×C), 153.3 (2×C), 137.3 (C), 137.2 (C), 137.0 (C), 136.8 (C), 135.8 (C), 124.9 (CH_2), 105.3 (2×CH), 104.9 (2×CH), 69.7 (CH_2), 60.9 (CH_3), 60.8 (CH_3), 56.3 (2×CH_3), 56.2 (2×CH_3), 55.8 (CH), 42.7 (CH); *m*/*z* (EI) 444 (M^+, 2), 347 (100), 318 (8); HRMS (ESI-TOF): MNa^+, found 467.1682. $C_{24}H_{28}O_8Na$ requires 467.1682.

4.12. 2-*epi*-Peperomin C (7)

Compound **6** (27 mg, 0.06 mmol) and Pd/C (2 mg) were dissolved in a mixture of dry benzene and pyridine (1:1 v/v, 1 mL) under an argon atmosphere. The argon inlet was replaced by a balloon filled with hydrogen gas, and the reaction mixture was stirred at room temperature. After the complete consumption of the starting material (20 min), the reaction mixture was filtered through Celite pad, and the residue was then washed with MeOH. Compound **7** was obtained as a white solid in 99% yield (26.5 mg, 90:10 dr). Recrystallization from EtOAc/hexanes gave compound **7** with 99% *ee* and 95:5 dr; R_f (40% EtOAc/hexanes) 0.16; $[\alpha]_D^{26}$ −67.7 (*c* 0.46, $CHCl_3$); mp 170–171 °C (EtOAc/hexanes); IR ($CHCl_3$): ν_{max} 1767, 1591, 1506, 1463, 1421, 1329, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.52 (s, 2H, Ar*H*), 6.43 (s, 2H, Ar*H*), 4.06–4.00 (m, 1H, C*H*H), 4.00–3.93 (m, 1H, CH*H*), 3.86 (s, 6H, 2×OCH_3), 3.84 (s, 6H, 2×OCH_3), 3.83 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.74 (d, *J*=12.0 Hz, 1H, C*H*), 3.47–3.34 (m, 1H, C*H*), 2.73 (dq, *J*=7.7, 7.6 Hz, 1H, C*H*), 1.14 (d, *J*=7.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.0 (CO), 153.6 (2×C), 153.2 (2×C), 137.4 (2×C), 137.1 (2×C), 104.4 (2×CH), 104.2 (2×CH), 70.5 (CH_2), 60.9 (CH_3), 60.8 (CH_3), 56.3 (2×CH_3), 56.2 (2×CH_3), 50.8 (CH), 43.2 (CH), 37.5 (CH), 10.5 (CH_3); *m*/*z* (EI) 446 (M^+, 1), 346 (100); HRMS (ESI-TOF): MNa^+, found 469.1833. $C_{24}H_{30}O_8Na$ requires 469.1838.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.07.101.

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