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An enantioselective total synthesis of (*S*)-(−)-licochalcone E: determination of the absolute configuration

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ABSTRACT

The absolute configuration of (−)-licochalcone E (**1**) was determined to be (*S*) via the first enantioselective total synthesis of the compound. The chirality in (*S*)-(−)-licochalcone E (**1**) was installed by asymmetric methylation of the Evans' oxazolidinone derivatives.

1. Introduction

Licochalcone E was isolated from the roots of *Glycyrrhiza inflata* during cytotoxicity-guided fractionation using the HT1080 cell line.[1] Further studies revealed that it possessed diverse biological activities, including the abilities to inhibit topoisomerase 1 and to induce endothelial cell apoptosis by modulating NF-kB and the Bcl-2 family.[2] Recently, it was reported that licochalcone E (**1**) also inhibited protein tyrosine phosphatase 1B.[3] The structure of licochalcone E was elucidated as (−)-(*E*)-3-[4-hydroxy-2-methoxy-5-(3-methylbut-3-en-2-yl)phenyl]-1-(4-hydroxyphenyl)prop-2-en-1-one (**1**) on the basis of spectral data, but its absolute configuration has not been reported.[1] Our interest in (−)-licochalcone E (**1**) was to determine the absolute stereochemistry and develop a highly versatile synthesis that might be suitable for analogs preparation. Herein, we describe the first enantioselective total synthesis and the determination of the absolute configuration of (*S*)-(−)-licochalcone E (**1**).

2. Results and discussion

Our overall synthetic strategy is outlined in Scheme 1. It was envisaged that (*S*)-(−)-licochalcone E (**1**) would be constructed via aldol condensation between the aldehyde **2** and properly protected 4-hydroxyacetophenone, followed by removal of both phenol protecting groups. The 2-allyl functionality of the 2-aryl-3-methylbut-3-ene **2** would be derived from carboxylic acid **3** through ketone formation followed by Wittig reaction. The chirality in **3** would be installed unambiguously by well established asymmetric methylation of the Evans' oxazolidinone **4**, which would be formed from aryl acetic acid **5**.[4] Compound **5**, in turn, would arise from 2,4-dihydroxybenzaldehyde by way of the bromide **6**.

The synthesis of key intermediate **4** from 2,4-dihydroxybenzaldehyde (**7**) is illustrated in Scheme 2. Bromination of **7** followed by selective MOM protection of 4-hydroxyl group provided 5-bromo-2-hydroxy-4-(methoxymethoxy)benzaldehyde (**6**), which was protected with MeI/K_2CO_3, to furnish the aldehyde **9** in 71% yield over three steps.[5] $NaBH_4$ reduction of the aldehyde **9** followed by TBS protection of the resulting alcohol gave [5-bromo-2-methoxy-4-(methoxymethoxy)benzyloxy](*tert*-butyl)dimethylsilane (**11**) in quantitative yield from **9**. With **11** in hand it was attempted to convert the TBS-protected bromide **11** to aryl acetic ester, the esterified product of the acid **5**, using palladium-catalyzed Negishi–Reformatsky coupling with an appropriate stannane.[7] Treatment of the bromide **11** with $PdCl_2[P(o\text{-tolyl})_3]_2$ (5–10 mol % of **11**), 1.2–2.0 equiv of ethyl tributylstannylacetate and vacuum dried 1.2–2.0 equiv of zinc bromide in DMF at 80–120 °C did not provide the ethyl ester of the acid **5**. So **11** was treated with *n*-BuLi and DMF at −78 °C to afford the aldehyde **12** in 85% yield.[6] Wittig reaction of the aldehyde **12** with methyltriphenylphosphoninum bromide in the presence of *n*-BuLi afforded the arylethene **13**, which was subjected to hydroboration with BH_3, followed by oxidative workup to give the alcohol **14** in 71% overall yield from **12**.[8] The resultant primary alcohol **14** was oxidized using Dess–Martin periodinane in methylene chloride to

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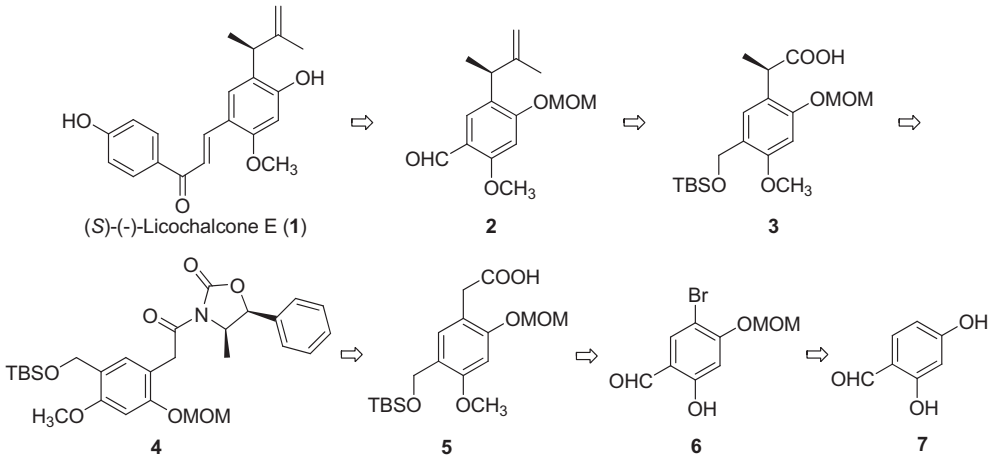
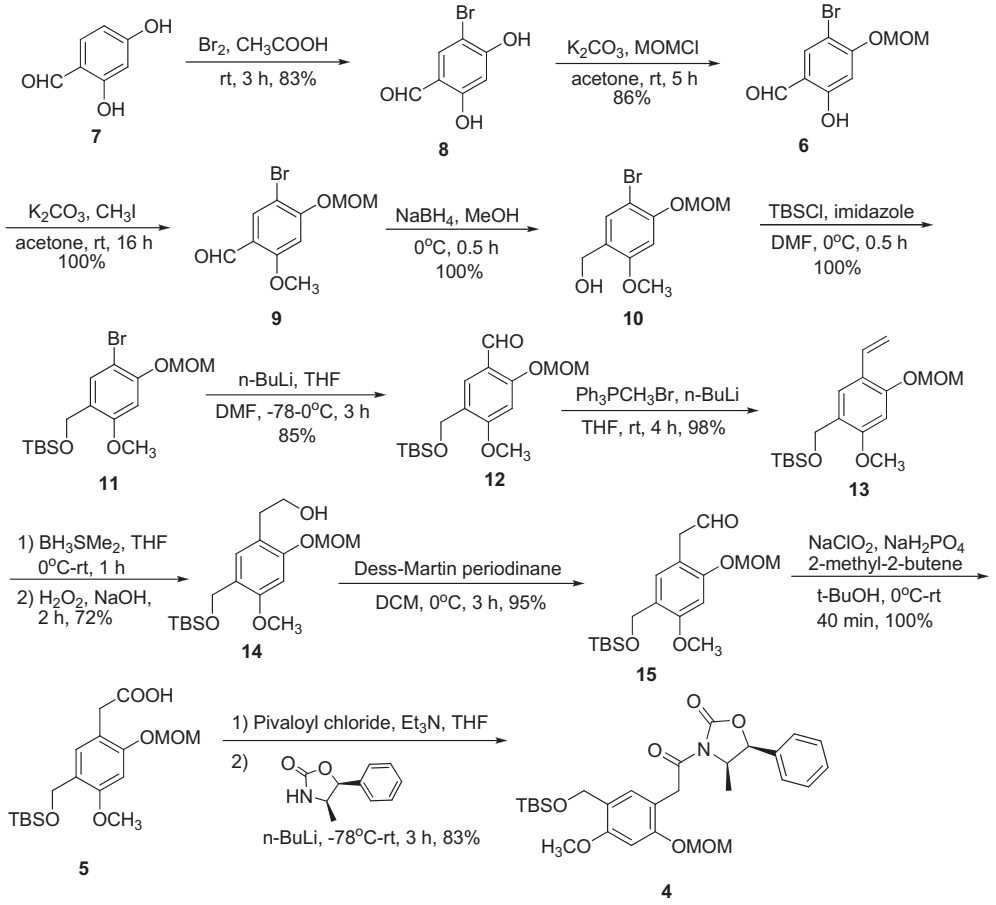


Scheme 1. Retrosynthesis of (*S*)-(−)-licochalcone E (**1**).

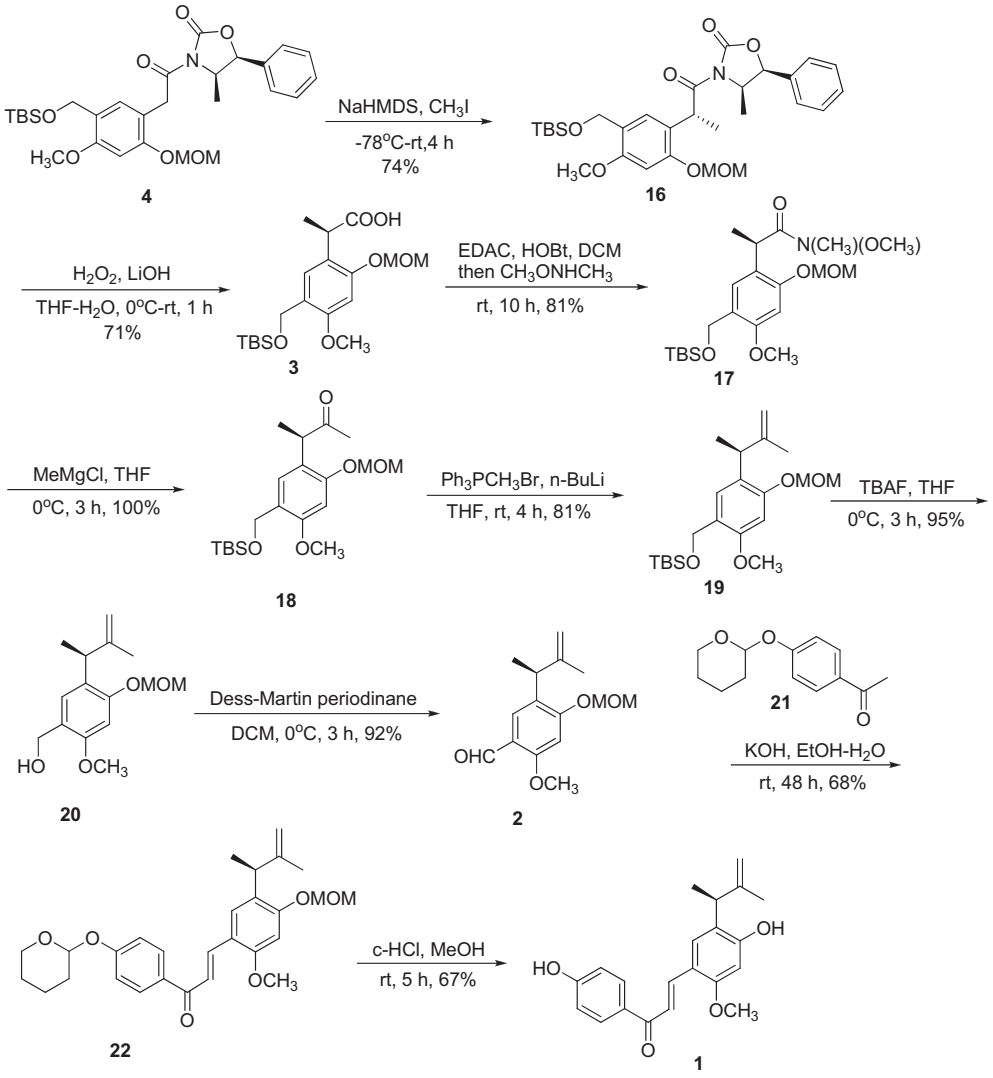


Scheme 2. Synthesis of key intermediate **4** from 2,4-dihroxybenzaldehyde (**7**).

give the aldehyde **15**, which was further oxidized using $NaClO_2$, NaH_2PO_4, *tert*-butanol, and 2-methyl-2-butene (Smith's conditions) to furnish the corresponding 2-aryl acetic acid **5** in 95% overall yield in two steps.[9]

2-Arylacetic acid **5** was reacted with pivaloyl chloride in the presence of triethylamine to give mixed anhydride, which was treated with the lithium anion of (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone to afford the imide **4** in 83% yield over two steps. (4*R*,5*S*)-(+)-4-Methyl-5-phenyl-2-oxazolidinone was chosen as a chiral auxiliary because it was proven to provide unambiguously defined absolute stereochemistry with high ee in asymmetric induction reaction.[4] Fortunately, it turned out that the imide **4** afforded the same enantiomer as the natural licochalcone E after subsequent reactions (vide infra).

With the key intermediate **4** in hand, we introduced necessary chirality to the molecule as shown in Scheme 3. The Evans' oxazolidinone derivative **4** was treated with NaHMDS and methyl iodide at −78 °C to afford methylated imide **16** in 74% yield, which was a single isomer by 300 MHz ^{1}H NMR. Hydrolysis of the Evans' oxazolidinone with LiOH and H_2O_2 provided acid **3** in 71% yield.[10]



Scheme 3. Synthesis of (*S*)-(−)-licochalcone E (**1**) from **4**.

2-Arylpropionic acid **3** was converted to 2-aryl-3-methylbut-3-ene **19** in three steps. Treatment of the chiral 2-arylpropionic acid **3** with EDAC, HOBt, followed by *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of triethylamine gave Weinreb's amide **17**, which was reacted with methyl magnesium chloride to furnish methyl ketone **18** in 81% overall yield from **3**.[11] This methyl ketone **18** underwent Wittig reaction with methyltriphenylphosphonium bromide in the presence of *n*-BuLi to afford 2-aryl-3-methylbut-3-ene **19**, which was treated with TBAF to give the alcohol **20** in 77% yield over two steps. Oxidation of alcohol **20** with Dess–Martin periodinane provided the key aldehyde **2** in 92% yield. Aldol condensation between the aldehyde **2** and tetrahydropyran-protected 4-hydroxyacetophenone[12] (**21**) in ethanolic KOH solution furnished protected licochalcone E (**22**), which was deprotected with concd HCl in methanol gave (−)-licochalcone E (**1**) in 46% yield over two steps.[13] NMR, MS, IR, and optical rotation {$[\alpha]_D^{25}$ −11.4 (*c* 1, acetone)} data of synthetic licochalcone E (**1**) were fully consistent with those for the natural (−)-licochalcone E.[1]

3. Conclusion

In conclusion, we have synthesized the natural (*S*) enantiomer of **1** through a stereochemically unambiguous route and have further proven its absolute configuration. Our work provided flexible and highly versatile approaches to synthesize not only (*S*)-(−)-licochalcone E (**1**) but also its analogs for biological testing.

4. Experimental section

4.1. General

Solvents were distilled under positive pressure of dry argon before use and dried by standard methods. Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl radical, triethylamine (Et_3N) was distilled over calcium hydride and stored over potassium hydroxide. (4*R*,5*S*)-(+)-4-Methyl-5-phenyl-2-oxazolidinone and (*S*)-(−)-4-benzyl-2-oxazolidinone were purchased from Alfa Aesar and Sigma–Aldrich, respectively. Unless otherwise noted, chemicals were obtained from local suppliers and were used without further purification. All reactions were performed under argon atmosphere and monitored by thin-layer chromatography (250 μ silica gel 60 F_{254} glass plates). Visualization was performed by ultraviolet light and/or by staining with 3% ethanol solution of phosphomolybdic acid. Infrared data were obtained on a JASCO, JP/FT-IR 300E infrared

spectrophotometer. NMR (^{1}H, ^{13}C) spectra were recorded on Varian Unity Plus 300 spectrometer. Low resolution mass spectra were obtained with a Shimadzu, JP/LCMS-2010 instrument. High resolution measurements were made with a Synapt HDMS (Waters, UK) instrument. Optical rotations were recorded in a 1 dm cell at 25 °C (JASCO, DiP-1000 digital polarimeter).

*4.1.1. 5-Bromo-2,4-dihydroxybenzaldehyde (**8**).* Bromine (3.78 mL, 72.4 mmol) was added dropwise to a solution of 2,4-dihydroxybenzaldehyde (**7**) (10.0 g, 72.4 mmol) in acetic acid (70.0 mL). After stirring for 3 h at room temperature, the resulting mixture was poured into water (100 mL), then the precipitated product was filtered and washed with water (100 mL), dried in vacuo, and the crude solids were recrystallized from a hot solution of 50% acetonitrile/toluene to yield 5-bromo-2,4-dihydroxybenzaldehyde (13.09 g, 83%. Mp: 165–168 °C).

*4.1.2. 5-Bromo-2-hydroxy-4-(methoxymethoxy)benzaldehyde (**6**).* To a mixture of 5-bromo-2,4-dihydroxybenzaldehyde (**8**) (7.07 g, 32.6 mmol), K_2CO_3 (13.6 g, 97.7 mmol) in anhydrous acetone (100 mL) was added chloromethyl methyl ether (2.52 mL, 32.3 mmol) dropwise at room temperature. After 5 h, the resulting mixture was filtered and the filtrate was concentrated under reduced pressure and the residue was then dissolved in EtOAc (50 mL), further washed with water (50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexanes/EtOAc=10:1) to give 5-bromo-2-hydroxy-4-(methoxymethoxy)benzaldehyde (**6**) (7.22 g, 86%) as a white crystalline solid. Mp: 59–62 °C. R_f=0.66 (3:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.70 (s, 1H, ArCHO), 7.69 (s, 1H, H6), 6.74 (s, 1H, H3), 5.30 (s, 2H, ArOC*H*$_2$OCH$_3$), 3.51 (s, 3H, ArOCH$_2$OC*H*$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 193.8, 163.1, 160.2, 137.4, 116.5, 103.4, 102.7, 94.8, 56.7. IR (KBr, neat): 3074, 3052, 2958, 2937, 2851, 1617, 1571, 1486, 1457, 1442, 1356, 1327, 1218, 1206, 1161, 1022, 966, 916, 832, 754, 742 cm^{-1}. LRMS (ESI): *m*/*z* 261 [M+H]$^+$. HRMS (ESI): calcd for $C_9H_9O_4Br$: 260.9586, found: 260.9605.

*4.1.3. 5-Bromo-2-methoxy-4-(methoxymethoxy)benzaldehyde (**9**).* A solution of 5-bromo-2-hydroxy-4-(methoxymethoxy)benzaldehyde (**6**) (6.10 g, 23.4 mmol) in dry acetone (70 mL) was added K_2CO_3 (9.73 g, 70.1 mmol) portionwise, followed by MeI (1.65 mL, 25.7 mmol) at room temperature. After 16 h, the reaction mixture was then filtered and the filtercake was washed with acetone (100 mL). The filtrate was concentrated under reduced pressure and the residue was dissolved in EtOAc (50 mL), washed with water (50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, and filtered and the filtrate was concentrated in vacuo to give 5-bromo-2-methoxy-4-(methoxymethoxy)benzaldehyde (**9**) (6.43 g, 100%) as a white crystalline solid. Mp: 70–73 °C. R_f=0.39 (3:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.26 (s, 1H, ArCHO), 8.01 (s, 1H, H6), 6.78 (s, 1H, H3), 5.33 (s, 2H, ArOC*H*$_2$OCH$_3$), 3.92 (s, 3H, ArOCH$_3$), 3.54 (s, 3H, ArOCH$_2$OC*H*$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 187.2, 162.2, 159.6, 132.8, 120.2, 104.1, 99.0, 95.0, 56.6, 55.9. IR (KBr, neat): 2968, 2945, 2866, 1667, 1601, 1503, 1470, 1450, 1420, 1398, 1323, 1287, 1204, 1164, 1104, 996, 943, 862, 815 cm^{-1}. LRMS (ESI): *m*/*z* 275 [M+H]$^+$. HRMS (ESI): calcd for $C_{10}H_{11}O_4BrNa$ [M+Na]$^+$: 296.9738, found: 296.9742.

*4.1.4. (5-Bromo-2-methoxy-4-(methoxymethoxy)phenyl)methanol (**10**).* To a stirred solution of 5-bromo-2-methoxy-4-(methoxymethoxy)benzaldehyde (**9**) (4.20 g, 15.3 mmol) in methanol (30 mL) was added $NaBH_4$ (0.49 g, 15.3 mmol) slowly at ice-bath temperature. After stirring for 30 min, the mixture was diluted with water (50 mL), extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure to give (5-bromo-2-methoxy-4-(methoxymethoxy)phenyl)methanol (**10**) (4.23 g, 100%) as a white solid. Mp: 68–71 °C. R_f=0.23 (3:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43 (s, 1H, H6), 6.76 (s, 1H, H3), 5.24 (s, 2H,ArOC*H*$_2$OCH$_3$), 4.59 (s, 2H, ArC*H*$_2$OH), 3.84 (s, 3H, ArOCH$_3$), 3.53 (s, 3H, ArOCH$_2$OC*H*$_3$), 2.16 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.3, 154.0, 132.4, 124.4, 102.7, 100.1, 95.3, 60.5, 56.3, 55.6. IR (KBr, neat): 3290, 2947, 2912, 2870, 1604, 1578, 1502, 1467, 1408, 1371, 1291, 1215, 1158, 1084, 1040, 1011, 922, 835 cm^{-1}. LRMS (ESI): *m*/*z* 278 [M+H]$^+$. HRMS (ESI): calcd for $C_{10}H_{13}O_4BrNa$ [M+Na]$^+$: 298.9895, found: 298.9907.

*4.1.5. (5-Bromo-2-methoxy-4-(methoxymethoxy)benzyloxy)(tert-butyl)dimethylsilane (**11**).* To a solution of (5-bromo-2-methoxy-4-(methoxymethoxy)phenyl)methanol (**10**) (4.20 g, 15.2 mmol) in DMF (20 mL) was added imidazole (4.14 g, 60.8 mmol) at ice-bath temperature followed by *tert*-butyldimethylsilyl chloride (TBSCl) (4.12 g, 27.4 mmol) and the mixture was stirred at this temperature for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10:1, hexanes/EtOAc) to give (5-bromo-2-methoxy-4-(methoxymethoxy)benzyloxy)(*tert*-butyl)-dimethylsilane (**11**) (5.93 g, 100%) as a colorless oil. R_f=0.59 (5:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55 (s, 1H, H6), 6.70 (s, 1H, H3), 5.22 (s, 2H, ArOC*H*$_2$OCH$_3$), 4.65 (d, 2H, *J*=0.9 Hz, H1a), 3.79 (s, 1H, ArOMe), 3.53 (s, 3H, ArOCH$_2$OC*H*$_3$), 0.95 [s, 9H, SiC(CH$_3$)$_3$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.0, 153.2, 130.9, 125.2, 103.0, 99.9, 95.5, 59.4, 56.3, 55.4, 25.9, 25.6, 18.4, 17.9, −5.4. IR (KBr, neat): 2955, 2930, 2898, 2857, 1604, 1498, 1463, 1371, 1300, 1256, 1215, 1155, 1088, 1005, 837, 777 cm^{-1}. LRMS (ESI): *m*/*z* 393 [M+H]$^+$. HRMS (ESI): calcd for $C_{16}H_{27}O_4BrSiNa$ [M+Na]$^+$: 413.0760, found: 413.0760.

*4.1.6. 5-((tert-Butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)benzaldehyde (**12**).* A 1.6 M solution of *n*-BuLi in hexane (19.0 mL, 30.7 mmol) was added dropwise to a solution of (5-bromo-2-methoxy-4-(methoxymethoxy)benzyloxy)(*tert*-butyl)dimethylsilane (**11**) (6.10 g, 15.6 mmol) in anhydrous THF (60 mL) at −78 °C under argon. After 1 h, dry DMF (9.50 mL, 122 mmol) was added dropwise. The reaction solution was then allowed to warm up to room temperature and stirring was continued for 2 h. The resulting solution was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (10:1, hexanes/EtOAc) to give 5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)benzaldehyde (**12**) (5.26 g, 85%) as a white solid. Mp: 66–69 °C. R_f=0.46 (4:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.34 (s, 1H, ArCHO), 7.93 (s, 1H, H6), 6.67 (s, 1H, H3), 5.29 (s, 2H, ArOCH$_2$OCH$_3$), 4.66 (d, 2H, *J*=0.6 Hz, H1a), 3.88 (s, 3H, ArOMe), 3.53 (s, 3H, ArOCH$_2$OCH$_3$), 0.95 [s, 9H, SiC(CH$_3$)$_3$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 188.2, 162.4, 161.0, 127.5, 124.1, 118.7, 97.0, 94.9, 59.7, 56.4, 55.5, 25.9, 18.4, −5.4. IR (KBr, neat): 2957, 2926, 2856, 1672, 1610, 1492, 1445, 1267, 1246, 1153, 1116, 1091, 1069, 855, 837, 778 cm^{-1}. LRMS (ESI): *m*/*z* 363 [M+Na]$^+$. HRMS (ESI): calcd for $C_{17}H_{28}O_5SiNa$ [M+Na]$^+$: 363.1604, found: 363.1607.

*4.1.7. tert-Butyl(2-methoxy-4-(methoxymethoxy)-5-vinylbenzyloxy)dimethylsilane (**13**).* To a suspension of Ph_3PCH_3Br (4.00 g, 11.2 mmol) in THF (50 mL) was added *n*-BuLi (1.6 M in hexane,

12.6 mL, 20.2 mmol) dropwise at room temperature and the mixture was stirred for 15 min. A solution of 5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)benzaldehyde (**12**) (3.80 g, 11.2 mmol) in THF (10 mL) was added dropwise to the reaction mixture. After stirring for additional 4 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with hexane (3×30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography (15:1, hexanes/EtOAc) to afford *tert*-butyl(2-methoxy-4-(methoxymethoxy)-5-vinylbenzyloxy)dimethylsilane (**13**) (3.70 g, 10.9 mmol, 98%) as a colorless oil. R_f=0.63 (5:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.59 (s, 1H, H6), 7.00 (q, 1H, J=17.7 Hz, H1″), 6.63 (s, 1H, H3), 5.65 [dd, 1H, J_1=1.5 Hz, J_2=17.7 Hz, H(2″-α)], 5.19 (s, 2H, ArOCH_2OCH$_3$), 5.14 [dd, 1H, J_1=1.5 Hz, J_2=11.1 Hz, H(2″-β)], 4.69 (s, 2H, H1a), 3.80 (s, 3H, ArOMe), 3.50 (s, 3H, ArOCH$_2$OCH_3), 0.96 [s, 9H, SiC(CH$_3$)$_3$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.7, 154.3, 131.0, 123.4, 119.5, 111.8, 98.1, 95.2, 59.9, 56.0, 55.2, 25.9, 18.4, −5.3. IR (KBr, neat): 3085, 2955, 2931, 2856, 1614, 1500, 1464, 1303, 1256, 1152, 1117, 1089, 1012, 840, 777 cm^{-1}. LRMS (ESI): m/z 339 [M+H]$^+$. HRMS (ESI): calcd for $C_{18}H_{30}O_4SiNa$ [M+Na]$^+$: 361.1811, found: 361.1815.

*4.1.8. 2-(5-((tert-Butyldimethylsilanyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)ethanol (**14**).* To a solution of *tert*-butyl (2-methoxy-4-(methoxymethoxy)-5-vinylbenzyloxy)dimethylsilane (**13**) (2.20 g, 6.50 mmol) in dry THF (20 mL) was added BH_3–SMe_2 (2.0 M in diethyl ether, 13.1 mL, 6.57 mmol) dropwise at 0 °C under argon. The reaction solution was allowed to warm up to room temperature and stirring was continued for 1 h before 2 N NaOH (4 mL) and 30% H_2O_2 (2 mL) were added. The mixture was further stirred for 2 h and diluted with saturated NH_4Cl (34 mL), then extracted with EtOAc (3×20 mL), and the combined organic layers were washed with brine (50 mL) and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (10:1 to 5:1, hexanes/EtOAc) to afford the 2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)ethanol (**14**) (1.67 g, 72%) as a colorless oil. R_f=0.35 (3:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.11 (s, 1H, H6), 6.57 (s, 1H, H3), 5.09 (s, 2H, ArOCH_2OCH$_3$), 4.58 (s, 2H, H1a), 3.71 (s, 2H, H2″), 3.69 (s, 3H, ArOMe), 3.39 (s, 3H, ArOCH$_2$OCH_3), 2.77 (t, 2H, J=6.6 Hz, H1″), 1.64 (s, 1H CH$_2$O*H*), 0.84 [s, 9H, SiC(CH$_3$)$_3$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.7, 155.1, 129.3, 123.0, 118.7, 98.1, 94.9, 63.2, 59.9, 56.1, 55.4, 33.4, 26.0, 18.5, −5.3. IR (KBr, neat): 3464, 3357, 2955, 2931, 2856, 1617, 1507, 1464, 1291, 1256, 1216, 1152, 1116, 1069, 1023, 837, 777 cm^{-1}. LRMS (ESI): m/z 379 [M+Na]$^+$. HRMS (ESI): calcd for $C_{18}H_{32}O_5SiNa$ [M+Na]$^+$: 379.1917, found: 379.1920.

*4.1.9. 2-(5-((tert-Butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)acetaldehyde (**15**).* To a stirring solution of 2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)ethanol (**14**) (1.20 g, 3.37 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C was added Dess–Martin periodinane (2.97 g, 7.01 mmol) slowly. After 3 h, the mixture was taken up in water (40 mL) and the aqueous layer was then extracted with Et_2O (3×50 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was further purified by chromatography on silica gel (10:1, hexanes/EtOAc) to give 2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)acetaldehyde (**15**) (1.14 g, 95%) as a colorless liquid. R_f=0.48 (3:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.67 (t, 1H, J=2.1 Hz, ArCH$_2$C*H*O), 7.20 (s, 1H, H6), 6.71 (s, 1H, H3), 5.17 (s, 2H, ArOCH_2OCH$_3$), 4.68 (s, 2H, H1a), 3.81 (s, 3H, ArOMe), 3.61 (d, 2H, J=2.1 Hz, ArCH_2CHO), 3.46 (s, 3H, ArOCH$_2$OCH_3), 0.94 [s, 9H, SiC(CH$_3$)$_3$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.5, 156.5, 155.2, 130.0, 123.3, 112.8, 97.7, 94.7, 60.0, 56.0, 55.4, 45.2, 26.0, 18.5, −5.3. IR (KBr, neat): 2955, 2930, 2899, 2856, 1726, 1617, 1508, 1465, 1152, 1117, 1070, 1023, 838, 777 cm^{-1}. LRMS (ESI): m/z 377 [M+Na]$^+$. HRMS (ESI): calcd for $C_{18}H_{30}O_5SiNa$ [M+Na]$^+$: 377.1760, found: 377.1760.

*4.1.10. 2-(5-((tert-Butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)acetic acid (**5**).* To a solution of 2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)acetaldehyde (**15**) (400 mg, 1.13 mmol) in *t*-BuOH (23.0 mL) was added 2-methyl-2-butene (6.50 mL) at 0 °C followed by a solution of $NaClO_4$ (746 mg, 8.25 mmol) and $NaH_2PO_4 \cdot H_2O$ (938 mg, 6.80 mmol) in H_2O (8 mL) dropwise. After 10 min, the reaction mixture was allowed to warm up to room temperature and stirred vigorously for 30 min. The reaction mixture was diluted with saturated aqueous NH_4Cl (10 mL) and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5:1, hexanes/EtOAc) to afford 2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)acetic acid (**5**) (416 mg, 100%) as a colorless oil. R_f=0.23 (3:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24 (s, 1H, H6), 6.68 (s, 1H, H3), 5.18 (s, 2H, ArOCH_2OCH$_3$), 4.67 (s, 2H, H1a), 3.79 (s, 3H, ArOMe), 3.46 (s, 3H, ArOCH$_2$OCH_3), 3.63 (s, 2H, ArCH_2COOH), 0.95 [s, 9H, SiC(CH$_3$)$_3$]. ^{13}C NMR ($CDCl_3$, 75 MHz): 177.9, 156.4, 154.9, 129.4, 122.9, 114.4, 97.8, 94.7, 59.8, 55.9, 55.3, 35.4, 29.7, 25.9, 18.6, −5.3. IR (KBr, neat): 2953, 2928, 2856, 1712, 1619, 1509, 1465, 1290, 1255, 1216, 1152, 1118, 1086, 1072, 1024, 837, 776 cm^{-1}. LRMS (ESI): m/z 393 [M+Na]$^+$. HRMS (ESI): calcd for $C_{18}H_{30}O_6SiNa$ [M+Na]$^+$: 393.1709, found: 393.1709.

*4.1.11. (4R,5S)-3-(2-(5-((tert-Butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)acetyl)-4-methyl-5-phenyloxazolidin-2-one (**4**).* To a solution of 2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)acetic acid (**5**) (1.50 g, 4.05 mmol), Et_3N (0.65 mL, 4.60 mmol) in anhydrous THF (15.0 mL) at −78 °C was added pivaloyl chloride (0.68 mL, 5.5 mmol) dropwise under an atmosphere of argon. The resulting mixture was stirred for 15 min at −78 °C and 1 h at 0 °C, then recooled to −78 °C. Meanwhile, *n*-BuLi (1.6 M in diethyl ether, 3.19 mL, 5.10 mmol) was added dropwise to a solution of (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone (0.90 g, 5.10 mmol) in anhydrous THF (10 mL) at −78 °C under an atmosphere of argon and the mixture was stirred for 40 min at −78 °C. The lithiated chiral auxiliary was then transferred into the reaction flask containing the preformed mixed anhydride via a cannula. After stirring for 15 min at −78 °C, the reaction mixture was allowed to warm up to room temperature for 2 h, then it was quenched with saturated aqueous NH_4Cl (30 mL), layers were separated and aqueous layer was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5:1, hexanes/EtOAc) to afford (4*R*,5*S*)-3-(2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)-acetyl)-4-methyl-5-phenyloxazolidin-2-one (**4**) (1.88 g, 83%) as a viscous oil. R_f=0.34 (4:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.40 (m, 5H, ArH), 7.20 (s, 1H, H6), 6.70 (s, 1H, H3), 5.70 (d, 1H, J=7.2 Hz, ArCH), 5.16 (d, 2H, J=0.3 Hz, ArOCH_2OCH$_3$), 4.78 (dq, 1H, J=7.2, 6.9 Hz, NCH), 4.68 (d, 2H, J=0.6 Hz, H1a), 4.24 (q, 2H, J=17.4 Hz, H1″), 3.80 (S, 3H, ArOMe), 3.46 (S, 3H, ArOCH$_2$OCH_3), 0.93 [s, 9H, SiC(CH$_3$)$_3$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.1, 156.2, 155.1, 153.2, 133.4, 129.3, 128.7, 128.6, 125.6, 122.9, 114.6, 97.9, 94.8, 78.9, 59.9, 55.9, 55.3, 54.9, 36.9, 26.0, 18.5, 14.5, −5.3. IR (KBr, neat): 2954, 2930, 2897, 2855, 1782, 1706, 1618, 1508, 1463, 1362, 1249, 1217, 1197, 1119, 1089, 1069, 1023, 838, 769 cm^{-1}.

LRMS (ESI): m/z 552 $[M+Na]^+$. HRMS (ESI): calcd for $C_{28}H_{39}O_7NSiNa$ $[M+Na]^+$: 552.2394, found: 552.2392. Optical rotation $[\alpha]_D^{20}$ −10.4 (c 1.0, CH_3Cl).

*4.1.12. (4R,5S)-3-((R)-2-(5-((tert-Butyldimethylsilyloxy)-methyl)-4-methoxy-2-(methoxymethoxy)-phenyl)-propanoyl)-4-methyl-5-phenyloxazolidin-2-one (**16**).* To a solution of (4*R*,5*S*)-3-(2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)acetyl)-4-methyl-5-phenyloxazolidin-2-one (**4**) (1.88 g, 3.55 mmol) in freshly distilled THF (20.0 mL) was added NaHMDS (1.0 M in THF, 4.10 mL, 4.10 mmol) at −78 °C under argon and the mixture was stirred at −78 °C for 1.2 h. A solution of MeI (0.90 mL, 14.5 mmol) in THF (1 mL) was added to the reaction mixture and the mixture was stirred for 4 h at −78 °C and warmed up to room temperature and further stirred for 2 h. The mixture was then quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5:1, hexanes/EtOAc) to give (4*R*,5*S*)-3-((*R*)-2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)propanoyl)-4-methyl-5-phenyloxazolidin-2-one (**16**) (1.42 g, 74%) as a viscous oil. R_f=0.46 (4:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28–7.43 (m, 5H, ArH), 7.25 (s, 1H, H6), 6.68 (s, 1H, H3), 5.52 (d, 1H, J=7.2 Hz, ArCH), 5.25 (dq, 1H, J=6.9, 6.6 Hz, NCH), 5.22 (d, 2H, J=1.5 Hz, $ArOCH_2OCH_3$), 4.70 (q, 1H, J=6.6 Hz, H1″), 4.69 (d, 2H, J=0.9 Hz, H1a), 3.79 (s, 3H, ArOMe), 3.54 (s, 3H, $ArOCH_2OCH_3$), 1.45 (d, 3H, J=6.9 Hz, H4″), 0.95 [s, 9H, $SiC(CH_3)_3$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.2, 155.8, 154.4, 152.3, 133.4, 128.9, 125.5, 125.4, 122.9, 121.3, 97.9, 95.1, 78.7, 59.9, 56.0, 55.4, 55.3, 37.7, 26.0, 18.4, 17.2, 14.5, −5.3. IR (KBr, neat): 2957, 2927, 2855, 1789, 1727, 1703, 1463, 1356, 1291, 1261, 1195, 1119, 1091, 836, 799 cm^{-1}. LRMS (ESI): m/z 566 $[M+Na]^+$. HRMS (ESI): calcd for $C_{29}H_{41}O_7NSiNa$ $[M+Na]^+$: 566.2550, found: 566.2552. Optical rotation $[\alpha]_D^{20}$ −31.6 (c 1.0, CH_3Cl).

*4.1.13. (R)-2-(5-((tert-Butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)-propanoic acid (**3**).* To a suspension of (4*R*,5*S*)-3-((*R*)-2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)propanoyl)-4-methyl-5-phenyloxazolidin-2-one (**16**) (230 mg, 0.42 mmol) in THF/H_2O (3.50 mL, v/v, 2:1) at 0 °C was added a solution of $LiOH\cdot H_2O$ (143 mg, 3.40 mmol) in H_2O (2.50 mL) dropwise, followed by a solution of 30% H_2O_2 (0.3 mL, 1.81 mmol). The mixture was allowed to warm up to room temperature and further stirred for 4 h. After evaporation of most of the solvent, the mixture was extracted with Et_2O (3×10 mL). The aqueous layer was then acidified with 10% HCl to pH 2–3 and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (3:1, hexanes/EtOAc) to afford (*R*)-2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)propanoic acid (**3**) (115 mg, 71%) as a colorless oil. R_f=0.16 (3:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33 (s, 1H, H6), 6.67 (s, 1H, H3), 5.19 (s, 2H, $ArOCH_2OCH_3$), 4.68 (d, 2H, J=1.5 Hz, H1a), 4.04 (q, 1H, J=6.9 Hz, H1″), 3.79 (s, 3H, ArOMe), 3.48 (s, 3H, $ArOCH_2OCH_3$), 1.48 (d, 3H, J=7.2 Hz, H4″), 0.94 [s, 9H, $SiC(CH_3)_3$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 180.9, 155.9, 154.2, 126.5, 123.2, 120.7, 97.8, 94.9, 59.9, 55.9, 55.3, 38.7, 25.9, 18.4, 16.9, −5.3. IR (KBr, neat): 3448, 2954, 2931, 2856, 1707, 1618, 1508, 1459, 1292, 1254, 1152, 1119, 1086,1006, 838, 776 cm^{-1}. LRMS (ESI): m/z 407 $[M+Na]^+$. HRMS (ESI): calcd for $C_{19}H_{32}O_6SiNa$ $[M+Na]^+$: 407.1866, found: 407.1867. Optical rotation $[\alpha]_D^{20}$ −15.0 (c 1.0, CH_3Cl).

*4.1.14. (R)-2-(5-((tert-Butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)-N-methoxy-N-methylpropanamide (**17**).* To a solution of (*R*)-2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)propanoic acid (**3**) (140 mg, 0.36 mmol) in dry CH_2Cl_2 (2.50 mL) were added EDCI (124 mg, 0.73 mmol), HOBt (60.0 mg, 0.45 mmol), Et_3N (0.06 mL, 0.43 mmol), and *N*,*O*-dimethylhydroxylamine hydrochloride (70.0 mg, 0.72 mmol) and the mixture was stirred at room temperature for 10 h. The resulting mixture was diluted with saturated aqueous NH_4Cl solution (5.0 mL), and aqueous layer was extracted with EtOAc (3×5.0 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (6:1, hexanes/EtOAc) to give (*R*)-2-[5-(*tert*-butyldimethylsilanyloxymethyl)-4-methoxy-2-methoxymethoxyphenyl]-*N*-methoxy-*N*-methylpropionamide (**17**) (125 mg, 81%) as a colorless oil. R_f=0.27 (3:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29 (s, 1H, H6), 6.65 (s, 1H, H3), 5.20 (s, 2H, $ArOCH_2OCH_3$), 4.67 (s, 2H, H1a), 3.78 (s, 3H, ArOMe), 3.49 (s, 3H, $NOCH_3$), 3.41 (s, 3H, $ArOCH_2OCH_3$), 3.14 (s, 3H, NCH_3), 1.36 (d, 3H, J=6.9 Hz, H4″), 0.93 [s, 9H, $SiC(CH_3)_3$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.7, 153.8, 126.8, 123.2, 122.5, 97.7, 94.9, 60.8, 60.0, 55.9, 55.3, 35.1, 25.9, 18.4, 17.9, −5.3 cm^{-1}. IR (KBr, neat): 2957, 2930, 2856, 1728, 1670, 1508, 1465, 1289, 1120, 1078, 1004, 839, 778 cm^{-1}. LRMS (ESI): m/z 450 $[M+Na]^+$. HRMS (ESI): calcd for $C_{21}H_{37}O_6NSiNa$ $[M+Na]^+$: 450.2288, found: 450.2285. Optical rotation $[\alpha]_D^{20}$ −50.2 (c 1.0, CH_3Cl).

*4.1.15. (R)-3-(5-((tert-Butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)-butan-2-one (**18**).* Under an atmosphere of argon, a solution of (*R*)-2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)-*N*-methoxy-*N*-methylpropanamide (**17**) (87.0 mg, 0.20 mmol) in anhydrous THF (3.0 mL) at 0 °C was added dropwise MeMgCl (3 M in diethyl ether, 0.15 mL, 0.45 mmol). The reaction mixture was maintained at this temperature for 3 h, then quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (15:1, hexanes/EtOAc) to afford (*R*)-3-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)butan-2-one (**18**) (78 mg, 100%) as a colorless oil. R_f=0.62 (3:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.19 (s, 1H, H6), 6.68 (s, 1H, H3), 5.19 (s, 2H, $ArOCH_2OCH_3$), 4.68 (d, 2H, J=0.9 Hz, H1a), 3.94 (q, 1H, J=7.2 Hz, H1″), 3.80 (s, 3H, ArOMe), 3.48 (s, 3H, $ArOCH_2OCH_3$), 1.56 (s, 3H, H3″), 1.34 (d, 3H, J=7.2 Hz, H4″), 0.94 [s, 9H, $SiC(CH_3)_3$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.7, 155.9, 154.3, 126.9, 123.4, 121.4, 97.7, 94.8, 59.9, 56.1, 55.3, 47.0, 27.9, 25.9, 18.4, 15.9, −5.3. IR (KBr, neat): 2954, 2931, 2897, 2856, 1715, 1615, 1505, 1464, 1290, 1256, 1216, 1152, 1119, 1087, 1011, 838, 777 cm^{-1}. LRMS (ESI): m/z 405 $[M+Na]^+$. HRMS (ESI): calcd for $C_{20}H_{34}O_5SiNa$ $[M+Na]^+$: 405.2073, found: 405.2073. Optical rotation $[\alpha]_D^{20}$ −123.2 (c 1.0, CH_3Cl).

*4.1.16. (S)-tert-Butyl(2-methoxy-4-(methoxymethoxy)-5-(3-methylbut-3-en-2-yl)benzyloxy)dimethylsilane (**19**).* To a suspension of Ph_3PCH_3Br (180 mg, 0.56 mmol) in THF (3.0 mL) was added *n*-BuLi (1.6 M in hexane, 0.34 mL, 0.55 mmol) dropwise at room temperature and the mixture was stirred for 15 min. A solution of (*R*)-3-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)butan-2-one (**18**) (95 mg, 0.25 mmol) in THF (0.5 mL) was added dropwise to the reaction mixture. After stirring for additional 4 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with hexane (4×5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (15:1, hexanes/EtOAc) to afford (*S*)-*tert*-butyl(2-methoxy-4-(methoxymethoxy)-5-(3-methylbut-3-en-2-yl)benzyloxy)dimethylsilane (**19**)

(76.5 mg, 81%) as a colorless oil. R_f=0.66 (5:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25 (s, 1H, H6), 6.63 (s, 1H, H3), 5.18 (d, 2H, J=1.2 Hz, $ArOCH_2OCH_3$), 4.85 (s, 2H, H5″), 4.69 (d, 2H, J=3.6 Hz, H1a), 4.28–4.29 (m, 1H, H1″), 3.79 (s, 3H, ArOMe), 3.49 (s, 3H, $ArOCH_2OCH_3$), 1.63 (s, 3H, H3″), 1.29 (d, 3H, J=7.2 Hz, H4″), 0.91 [s, 9H, $SiC(CH_3)_3$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.9, 154.3, 149.3, 125.9, 125.7, 123.0, 109.4, 97.9, 95.1, 60.0, 55.9, 55.3, 37.9, 25.9, 22.2, 19.6, −5.3. IR (KBr, neat): 3084, 2956, 2929, 2856, 1615, 1504, 1464, 1291, 1254, 1151, 1117, 1083, 1061, 1025, 1011, 838, 776 cm^{-1}. LRMS (ESI): m/z 381 $[M+H]^+$. HRMS (ESI): calcd for $C_{21}H_{36}O_4SiNa$ $[M+Na]^+$: 403.2281, found: 403.2282. Optical rotation $[\alpha]_D^{20}$ −40.7 (c 1.0, CH_3Cl).

*4.1.17. (S)-2-Methoxy-4-(methoxymethoxy)-5-(3-methylbut-3-en-2-yl)phenylmethanol (**20**).* A solution of (*S*)-*tert*-butyl(2-methoxy-4-(methoxymethoxy)-5-(3-methylbut-3-en-2-yl)benzyloxy)dimethylsilane (**19**) (80.0 mg, 0.21 mmol) in THF (3.50 mL) was treated with tetra-*n*-butylammonium fluoride (165 mg, 0.63 mmol) at 0 °C. After stirring for 3 h at 0 °C, the resulting mixture was diluted with saturated aqueous NH_4Cl solution (5 mL), and extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel (5:1, hexanes/EtOAc) to give (*S*)-2-methoxy-4-(methoxymethoxy)-5-(3-methylbut-3-en-2-yl)phenylmethanol (**20**) (53.1 mg, 95%) as a colorless oil. R_f=0.21 (3:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.00 (s, 1H, H6), 6.69 (s, 1H, H3), 5.19 (d, 2H, J=0.6 Hz, $ArOCH_2OCH_3$), 4.84 (d, 1H, J=4.2 Hz, H5″), 4.60 (d, 2H, J=4.2 Hz, H1a), 3.85 (s, 3H, ArOMe), 3.49 (s, 3H, $ArOCH_2OCH_3$), 3.76 (q, 1H, J=7.2 Hz H1″), 1.63 (s, 3H, H3″), 1.28 (d, 3H, J=6.9 Hz, H4″). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.6, 155.2, 149.1, 127.9, 125.9, 122.3, 109.5, 98.3, 94.8, 62.0, 55.9, 55.4, 37.8, 22.3, 19.6. IR (KBr, neat): 3512, 2961, 2929, 2873, 1727, 1504, 1465, 1289, 1193, 1151, 1116, 1079, 1060, 1023 cm^{-1}. LRMS (ESI): m/z 289 $[M+Na]^+$. HRMS (ESI): calcd for $C_{15}H_{22}O_4Na$ $[M+Na]^+$: 289.1416, found: 289.1416. Optical rotation $[\alpha]_D^{20}$ −84.4 (c 1.0, CH_3Cl).

*4.1.18. (S)-2-Methoxy-4-(methoxymethoxy)-5-(3-methylbut-3-en-2-yl)benzaldehyde (**2**).* To a stirring solution of (*S*)-(2-methoxy-4-(methoxymethoxy)-5-(3-methylbut-3-en-2-yl)phenylmethanol (**20**) (18.0 mg, 0.07 mmol) in dry CH_2Cl_2 (1.5 mL) at 0 °C was added Dess–Martin periodinane (80.0 mg, 0.20 mmol) slowly. After 3 h, the mixture was taken up in water (5.0 mL) and the aqueous layer was extracted with Et_2O (4×5 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (8:1, hexanes/EtOAc) to give (*S*)-2-methoxy-4-(methoxymethoxy)-5-(3-methylbut-3-en-2-yl)benzaldehyde (**2**) (15.6 mg, 92%) as a colorless liquid. R_f=0.47 (3:1 hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.31 (s, 1H, ArCHO), 7.65 (s, 1H, H6), 6.69 (s, 1H, H3), 5.28 (d, 2H, J=2.7 Hz, $ArOCH_2OCH_3$), 4.84 (d, 2H, J=9.9 Hz, H5″), 3.91 (s, 3H, ArOMe), 3.74 (q, 1H, J=7.5 Hz, H1″), 3.49 (s, 3H, $ArOCH_2OCH_3$), 1.62 (s, 3H, H3″), 1.31 (d, 3H, J=7.2 Hz, H4″). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 188.6, 162.2, 161.1, 148.3, 127.8, 126.9, 119.0, 110.2, 97.2, 94.1, 56.3, 55.7, 38.1, 21.9, 19.2. IR (KBr, neat): 2964, 2927, 2854, 1676, 1606, 1493, 1459, 1450, 1270, 1152, 1119, 1001 cm^{-1}. LRMS (ESI): m/z 265 $[M+H]^+$. HRMS (ESI): calcd for $C_{15}H_{20}O_4Na$ $[M+Na]^+$: 287.1259, found: 287.1265. Optical rotation $[\alpha]_D^{20}$ −57.4 (c 1.0, CH_3Cl).

*4.1.19. (E)-3-(2-Methoxy-4-(methoxymethoxy)-5-((S)-3-methylbut-3-en-2-yl)phenyl)-1-(4-(tetrahydro-2H-pyran-2-yloxy)phenyl)prop-2-en-1-one (**22**).* To a solution of (*S*)-2-methoxy-4-(methoxymethoxy)-5-(3-methylbut-3-en-2-yl)-benzaldehyde (**2**) (8.00 mg, 0.03 mmol) and 1-(4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl)-ethanone (**21**) (14.0 mg, 0.06 mmol) in EtOH and H_2O (1.2 mL, v/v 2:1) at room temperature was added dropwise a solution of KOH (28.0 mg, 0.51 mmol) in H_2O (0.5 mL). The reaction mixture was stirred at room temperature for 48 h and the resulting mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was further purified by chromatography on silica gel (5:1, hexanes/EtOAc) to afford (*E*)-3-(2-methoxy-4-(methoxymethoxy)-5-((*S*)-3-methylbut-3-en-2-yl)phenyl)-1-(4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl)prop-2-en-1-one (**22**) (9.50 mg, 68%) as a yellow power. Mp: 73–77 °C. R_f=0.45 (3:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.01 (dd, 3H, J=8.7 Hz, J=15.9 Hz, H2′, H6′, H1a), 7.53 (d, 1H, J=15.9 Hz, H1β), 7.38 (s, 1H, H6), 7.12 (d, 2H, J=9.0 Hz, H3′5′), 6.71 (s, 1H, H3), 5.53 (t, 1H, J=3 Hz, THP), 5.25 (s, 2H, $ArOCH_2OCH_3$), 4.88 (d, 2H, J=8.7 Hz, H5″), 3.90 (s, 3H, ArOMe), 3.57–3.88 (m, 3H, THP H1″), 3.50 (s, 3H, $ArOCH_2OCH_3$), 1.68–1.92 (m, 6H, THP), 1.57 (S, 3H, H3″), 1.33 (d, 3H, J=7.2 Hz, H4″). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.9, 160.5, 158.5, 157.6, 148.8, 140.1, 132.3, 130.5, 128.8, 126.5, 120.7, 117.5, 115.9, 115.7, 109.9, 97.9, 96.0, 94.3, 62.0, 56.1, 55.7, 37.9, 30.1, 25.1, 22.2, 19.5, 18.5. IR (KBr, neat): 2959, 2917, 2849, 1769, 1599, 1501, 1464, 1451, 1281, 1219, 1192, 1164, 1119, 1006 cm^{-1}. LRMS (ESI): m/z 489 $[M+Na]^+$. HRMS (ESI): calcd for $C_{28}H_{34}O_6Na$ $[M+Na]^+$: 489.2253, found: 489.2259. Optical rotation $[\alpha]_D^{20}$ −34.9 (c 1.0, CH_3Cl).

*4.1.20. (S)-Licochalcone E (**1**).* To a solution of (*E*)-3-(2-methoxy-4-(methoxymethoxy)-5-((*S*)-3-methylbut-3-en-2-yl)-phenyl)-1-(4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl)prop-2-en-1-one (**22**) (5.00 mg, 0.01 mmol) in dry MeOH (1.5 mL) was added 10 drops of concentrated HCl. The reaction mixture was stirred at room temperature for 5 h, then quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (3:1, hexanes/EtOAc) to afford (*S*)-licochalcone E (**1**) (2.90 mg, 67%) as a yellow power. Mp: 76–80 °C. R_f=0.28 (1:1 v/v hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.01 (d, 1H, J=15.6 Hz, H-β), 7.97 (d, 2H, J=9.0 Hz, H-2′,6′), 7.62 (d, 1H, J=15.6 Hz, H-α), 7.52 (s, 1H, H6), 6.93 (d, 2H, J=9.0 Hz, H-3′5′), 6.61 (s, 1H, H3), 4.89 (d, 2H, J=7.2 Hz, H-5″), 3.88 (s, 3H, ArOMe), 3.79 (m, 1H, H-1″), 1.67 (s, 3H, H-3″), 1.34 (d, 3H, J=7.2 Hz, H-4″). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 188.5, 162.4, 159.6, 159.3, 149.9, 139.9, 131.8, 131.6, 129.4, 125.0, 119.6, 116.6, 110.2, 99.9, 56.0, 38.7, 22.4, 19.7. IR (KBr, neat): 3440, 1716, 1645, 1603, 1509, 1448, 1288, 1261, 1216, 1168, 1121, 1036 cm^{-1}. LRMS (ESI): m/z 339 $[M+H]^+$. HRMS (ESI): calcd for $C_{21}H_{23}O_4$ $M+H]^+$: 339.1596, found: 339.1593. Optical rotation $[\alpha]_D^{20}$ −11.4 (c 1.0, acetone).[14]

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Supplementary data

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13. Enantiomeric excess of the synthetic (*S*)-(−)-licochalcone E (**1**) can be readily determined by HPLC on a Chiracel OJ column detecting at 254 nm (0.1% formic acid in hexane/0.1% formic acid in isopropanol=90:10; (*S*) enantiomer 41.9 min; (*R*) enantiomer 44.1 min) and was found to be 96% ee by integration.
14. Spectral data of isolated (*S*)-(−)-licochalcone E. Amorphous powder; $[\alpha]_D$ −11.9 (*c* 0.1, MeOH); ^{1}H NMR (acetone-d_6, 300 MHz) δ 1.33 (3H, d, *J*=7.2 Hz, H-4″), 1.67 (3H, s, H-5″), 3.82 (3H, s, OMe), 3.87 (1H, m, H-1″), 4.87 (1H, br s, H-3″a), 4.90 (1H, br s, H-3″b), 6.59 (1H, s, H-3), 6.89 (2H, d, *J*=8.7 Hz, H-3′, 5′), 7.43 (1H, s, H-6), 7.57 (1H, d, *J*=15.5 Hz, H-α), 7.93 (2H, d, *J*=8.7 Hz, H-2′,6′), 8.00 (1H, d, *J*=15.5 Hz, H-β). ^{13}C NMR (acetone-d_6, 125 MHz) δ: 187.5 (C=O), 162.9 (C-4′), 159.7 (C-4), 158.8 (C-2), 149.2 (C-2″), 139.0 (C-β), 130.6 (C-2′, C-6′), 130.0 (C-1′), 128.3 (C-6), 124.3 (C-5), 118.1 (C-α), 115.5 (C-3′, C-5′), 114.9 (C-1), 109.1 (C-3″), 99.1 (C-3), 55.0 (OMe), 37.7 (C-1″), 21.5 (C-5″), 18.8 (C-4″).