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Stereoselective Total Synthesis of (+)-Licochalcone E

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The synthesis of (+)-licochalcone E (**1**) was accomplished for the first time in 13 steps from aryl bromide (**6**) with 8% overall yield. Palladium-catalyzed Negishi-Reformatsky coupling reaction of compound **6** with ethyl 2-(tributylstannyl)acetate provided the aryl acetic ester (**5**), which was converted to aryl acetamide (**4**) via mixed anhydride formation. Chiral auxiliary-mediated methylation of the (*S*)-4-benzyl-2-oxazolidinone-derived aryl acetamide (**4**) provided the key asymmetric benzylic methyl group in compound **1**.

Key words: (+)-Licochalcone E, Negishi-Reformatsky reaction, Retrochalcone

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INTRODUCTION

Licorice is the roots and stolons of certain *Glycyrrhiza* species such as *G. inflata* and *G. uralensis*. Licorice is a popular food additive used worldwide as a sweetener in tobaccos, chewing gums, and candies, but it is also one of the most widely used medicinal herbs with anti-tumorigenic, antimicrobial, antiulcer, and antioxidant activities (Nomura and Fukai, 1998). Recently, (–)-licochalcone E was isolated from the roots of *G. inflata* during cytotoxicity-guided fractionation using the HT1080 cell line (Yoon et al., 2005). In addition to cytotoxicity, it possessed diverse biological activities, including the abilities to inhibit topoisomerase 1 (Yoon et al., 2007), to inhibit protein tyrosine phosphatase 1B (Yoon et al., 2009a), and to induce endothelial cell apoptosis by modulating NF-κB and the Bcl-2 family (Chang et al., 2007). It was also reported that (–)-licochalcone E had vasorelaxing effects (Yoon et al., 2010). We chose to synthesize the unnatural enantiomer, (+)-licochalcone E (**1**), since the natural product can be synthesized in a divergent fashion from a late-stage intermediate derived from the arylacetate (**5**). Although the racemic mixture and the natural (–)-licochalcone E have been synthesized before (Na et al., 2009; Yoon et al., 2009b; Liu et al., 2010), synthesis of (+)-licochalcone E (**1**) has never been reported. The synthetic route described here gives access to (+)-licochalcone E (**1**) and its derivatives in a more concise and high-yielding fashion and this will contribute to the ongoing search for their molecular target. Herein, we describe the first enantioselective total synthesis of (+)-licochalcone E (**1**).

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MATERIALS AND METHODS

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, and triethylamine (Et_3N) was distilled over calcium hydride and stored over potassium hydroxide. (*S*)-(–)-4-Benzyl-2-oxazolidinone was purchased from Sigma-Aldrich. 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 micron 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 spec-

trophotometer. 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) instrument. Optical rotations were recorded in a 1 dm cell at 25°C (JASCO, DiP-1000 digital polarimeter).

Ethyl (5-(*tert*-butyldimethylsilanyloxymethyl)-4-methoxy-2-methoxymethoxyphenyl)-acetate (5)

Zinc bromide (1.56 g, 6.92 mmol) in a dry flask was heated at 140°C for 1 h under high vacuum. Then a mixture of (5-bromo-2-methoxy-4-methoxymethoxy-benzyloxy)-*tert*-butyldimethylsilane (**6**) (1.93 g, 4.94 mmol), α-(tributylstannyl)acetate (2.61 g, 6.92 mmol), and $PdCl_2(o\text{-}tol_3P)_2$ (310 mg, 0.395 mmol) in dry DMF (10 mL) was added to the flask and heated at 80°C for 14 h under argon. The black reaction mixture was diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was further purified by flash chromatography on silica gel (15:1, hexanes-EtOAc) to give **5** (1.41 g, 3.58 mmol, 72%) as a pale yellow oil. R*f* = 0.43 (3:1 v/v hexanes-EtOAc). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.23 (s, 1H, H6), 6.67 (s, 1H, H3), 5.16 (s, 2H, $ArOC\underline{H}_2OCH_3$), 4.68 (d, 2H, *J* = 3.9 Hz, $ArC\underline{H}_2OTBS$), 4.14 (q, 2H, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$), 3.79 (s, 1H, ArOMe), 3.58 (s, 2H, $ArC\underline{H}_2COOEt$), 3.49 (s, 3H, $ArOCH_2OC\underline{H}_3$), 1.24 (t, 3H, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 0.94 [(s, 9H, $SiC(CH_3)_3$]. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 172.1, 156.1, 155.0, 129.3, 122.9, 115.2, 97.9, 94.8, 60.5, 59.9, 55.9, 55.3, 35.6, 25.9, 18.4, 14.2, –5.3. IR (KBr, neat): 2955, 2931, 2903, 2855, 1737, 1618, 1509, 1465, 1254, 1215, 1191, 1153, 1116, 1091, 1073, 1021, 996, 838, 776 cm^{-1}. LRMS (ESI): *m/z* 421 $[M+Na]^+$. HRMS (ESI): calcd for $C_{20}H_{34}O_6SiNa$ $[M+Na]^+$: 421.2101, found: 421.2101.

(*S*)-4-Benzyl-3-(2-(5-((tert-butyldimethylsilyloxy) methyl)-4-methoxy-2-(methoxy-methoxy)phenyl) acetyl)oxazolidin-2-one (4)

A solution of ethyl (5-(*tert*-butyldimethylsilanyloxy-methyl)-4-methoxy-2-methoxymethoxyphenyl)acetate (**5**) (110 mg, 0.28 mmol) in EtOH (3 mL) was added 1 N NaOH dropwise. The solution was heated to 40°C and stirred for 16 h, the reaction solution was allowed to cool to room temperature and concentrate under reduced pressure. The residue was then acidified with 5% HCl to pH 3~4 and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was further purified by flash chromatography (3:1, hexanes-EtOAc) to give (5-(*tert*-butyldimethylsilanyl-oxymethyl)-4-methoxy-2-methoxymethoxyphenyl)acetic acid (102 mg, 0.28 mmol, 99%) 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, $ArOC\underline{H}_2OCH_3$), 4.67 (s, 2H, $ArC\underline{H}_2OTBS$), 3.79 (s, 3H, $ArOC\underline{H}_3$), 3.46 (s, 3H, $ArOCH_2OC\underline{H}_3$), 3.63 (s, 2H, $ArC\underline{H}_2COOH$), 0.95 [s, 9H, $SiC(CH_3)_3$]. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 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.

To a solution of (5-(*tert*-butyldimethylsilanyloxy-methyl)-4-methoxy-2-methoxymethoxyphenyl)acetic acid (860 mg, 2.40 mmol), and Et_3N (0.38 mL, 2.64 mmol) in anhydrous THF (10 mL) at –78°C was added pivaloyl chloride (0.4 mL, 3.12 mmol) dropwise under an atmosphere of argon. The resulting mixture was stirred for 15 min at –78°C, 1 h at 0°C, then recooled to –78°C. Meanwhile, in a different flask, *n*-BuLi (1.8 mL of 1.6 M in diethyl ether, 2.9 mmol) was added dropwise to a solution of (*S*)-(–)-4-benzyl-2-oxazolidi-none (518 mg, 2.92 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, it was then transferred into the reaction flask containing the preformed mixed anhydride via a cannula. After stirring the reaction mixture for 15 min, it was allowed to warm up to room temperature for 2 h then quenched with saturated aqueous NH_4Cl (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (4:1, hexanes-EtOAc) to afford **4** (1.01 g, 1.95 mmol, 81%) as a viscous oil. R*f* = 0.38 (3:1 v/v hexanes-EtOAc). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.20-7.36 (m, 5H, ArH), 7.22 (s, 1H, H6), 6.72 (s, 1H, H3), 5.18 (d, 2H, *J* = 1.5 Hz, $ArOC\underline{H}_2OCH_3$), 4.69 (s, 2H, $ArC\underline{H}_2OTBS$), 4.66-4.73 (m, 1H, NCH), 4.13-4.35 (m, 4H, $ArC\underline{H}_2CON$, $NCHC\underline{H}_2O$), 3.81 (s, 3H, $ArOCH_3$), 3.47 (s, 3H, $ArOCH_2OC\underline{H}_3$), 3.28 (dd, 1H, *J* = 3.3, 13.2 Hz, ArCH), 2.82 (dd, 1H, *J* = 9.3, 13.2 Hz, ArCH), 0.94 [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 $C_{28}H_{39}O_7NSiNa$ $[M+Na]^+$: 552.2397, found: 552.2394. Optical rotation $[\alpha]^{20}_D$ = +60.7 (*c* = 1.0, $CHCl_3$).

(*S*)-4-Benzyl-3-((*S*)-2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxy-methoxy) phenyl)propanoyl)oxazolidin-2-one (7)

To a solution of (*S*)-4-benzyl-3-(2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy) phenyl)acetyl)oxazolidin-2-one (**4**) (0.88 g, 1.66 mmol) in freshly distilled THF (10 mL) was added NaHMDS (1.90 mL of 1.0 M in THF, 1.90 mmol) at −78°C under argon and the mixture was stirred for 1.2 h. A solution of MeI (0.41 mL, 6.64 mmol) in THF (1 mL) was added dropwise to the reaction mixture and stirring was continued for 4 h at −78°C. The reaction mixture was allowed to warm up to room temperature and stirred for an additional 2 h. It 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), 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 **7** (0.68 g, 1.25 mmol, 74%) as a viscous oil. R*f* = 0.39 (3:1 v/v hexanes-EtOAc). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.24-7.40 (m, 5H, ArH), 7.26 (s, 1H, H6), 6.69 (s, 1H, H3), 5.21 (d, 2H, *J* = 3.9 Hz, $ArOC\underline{H}_2OCH_3$), 4.72 (s, 2H, $ArC\underline{H}_2OTBS$), 4.64-4.73 (m, 1H, NCH), 4.08-4.18 (m, 2H, $NCHC\underline{H}_2O$), 3.82 (s, 3H, $ArOCH_3$), 3.53 (s, 3H, $ArOCH_2OC\underline{H}_3$), 3.39 (dd, 1H, *J* = 3.3, 13.2 Hz, ArCH), 2.82 (dd, 1H, *J* = 9.9, 13.2 Hz, ArCH), 1.53 (d, 3H, *J* = 6.9 Hz, $ArCH(C\underline{H}_3)$), 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: 566.2550. Optical rotation $[\alpha]^{20}_D$ = +93.8 (*c* = 1.0, $CHCl_3$).

(*S*)-2-(5-((*tert*-Butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)-propanoic acid (3)

To a suspension of (*S*)-4-benzyl-3-((*S*)-2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxy-methoxy)phenyl)propanoyl)-oxazolidin-2-one (**7**) (460 mg, 0.84 mmol) in THF-H_2O (7 mL, v/v, 2:1) at 0°C was added a solution of $LiOH{\cdot}H_2O$ (286 mg, 6.8 mmol) in H_2O (5 mL) dropwise, followed by a solution of 30% H_2O_2 (0.6 mL, 3.6 mmol). The mixture was allowed to warm up to room temperature and stirred for an additional 4 h. After evaporation of most of the solvent, the mixture was extracted with Et_2O (3 × 15 mL). The aqueous layer was then acidified with 10% HCl to pH 2~3 and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (3:1, hexanes-EtOAc) to afford **3** (230 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, $ArOC\underline{H}_2OCH_3$), 4.68 (d, 2H, *J* = 1.5 Hz, $ArC\underline{H}_2OTBS$), 4.04 (q, 1H, *J* = 6.9 Hz, $ArC\underline{H}(CH_3)$), 3.79 (s, 3H, ArOMe), 3.48 (s, 3H, $ArOCH_2OC\underline{H}_3$), 1.48 (d, 3H, *J* = 7.2 Hz, $ArCH(C\underline{H}_3)$), 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: 407.1874. Optical rotation $[\alpha]^{20}_D$ = +13.7 (*c* = 1.0, $CHCl_3$).

(*S*)-2-(5-((*tert*-Butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)-*N*-methoxy-*N*-methylpropanamide (8)

To a solution of (*S*)-2-(5-((*tert*-butyldimethylsilyloxy) methyl)-4-methoxy-2-(methoxymethoxy)phenyl)propanoic acid (**3**) (210 mg, 0.54 mmol) in dry CH_2Cl_2 (4 mL) was added EDCI (186 mg, 1.1 mmol), HOBt (90 mg, 0.68 mmol), Et_3N (0.09 mL, 0.65 mmol), and *N*,*O*-dimethylhydroxylamine hydrochloride (105 mg, 0.11 mmol) and the mixture was stirred at room temperature for 10 h. The resulting mixture was diluted with saturated aqueous NH_4Cl solution (8 mL), and aqueous layer was extracted with EtOAc (3 × 8 mL). The combined organic layers were washed with brine (25 mL), 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 **8** (188 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, $ArOC\underline{H}_2OCH_3$), 4.67 (s, 2H, $ArC\underline{H}_2OTBS$), 3.78 (s, 3H, ArOMe), 3.49 (s, 3H, $NOC\underline{H}_3$), 3.41 (s, 3H, $ArOCH_2OC\underline{H}_3$), 3.14 (s, 3H, NCH_3), 1.36 (d, 3H, *J* = 6.9 Hz, $ArCH(C\underline{H}_3)$), 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. 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: 450.2292. Optical rotation $[\alpha]_D^{20}$ = +62.0 (*c* = 1.0, $CHCl_3$).

(*S*)-3-(5-((*tert*-Butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)-butan-2-one (9)

Under an atmosphere of argon, a solution of (*S*)-2-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)-*N*-methoxy-*N*-methylpropanamide (**8**) (174 mg, 0.4 mmol) in anhydrous THF (6 mL) at 0°C was added dropwise to a solution of MeMgCl (3 M in diethyl ether, 0.3 mL, 0.9 mmol). The reaction mixture was maintained at this temperature for 3 h, then quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL), 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 **9** (156 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, $ArOC\underline{H}_2OCH_3$), 4.68 (d, 2H, *J* = 0.9 Hz, $ArC\underline{H}_2OTBS$), 3.94 (q, 1H, *J* = 7.2 Hz, $ArC\underline{H}(CH_3)$), 3.80 (s, 3H, $ArOCH_3$), 3.48 (s, 3H, $ArOCH_2OC\underline{H}_3$), 1.56 (s, 3H, $COC\underline{H}_3$), 1.34 (d, 3H, *J* = 7.2 Hz, $ArCH(C\underline{H}_3)$), 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, 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 $[\alpha]_D^{20}$ = +117.8 (*c* = 1.0, $CHCl_3$).

(*R*)-*tert*-Butyl(2-methoxy-4-(methoxymethoxy)-5-(3-methylbut-3-en-2-yl)benzyloxy)-dimethylsilane (10)

To a suspension of Ph_3PCH_3Br (360 mg, 1.12 mmol) in THF (6 mL) was added *n*-BuLi (1.6 M in hexane, 0.68 mL, 1.1 mmol) dropwise at room temperature and the mixture was stirred for 15 min. A solution of (*S*)-3-(5-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-2-(methoxymethoxy)phenyl)butan-2-one (**9**) (190 mg, 0.5 mmol) in THF (1 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 (10 mL) and extracted with hexane (4 × 10 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 **10** (153 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, $ArOC\underline{H}_2OCH_3$), 4.85 (s, 2H, $C(=C\underline{H}_2)CH_3$), 4.69 (d, 2H, *J* = 3.6 Hz, $ArC\underline{H}_2OTBS$), 4.28-4.29 (m, 1H, $ArC\underline{H}(CH_3)$), 3.79 (s, 3H, $ArOCH_3$), 3.49 (s, 3H, $ArOCH_2OC\underline{H}_3$), 1.63 (s, 3H, $C(=CH_2)C\underline{H}_3$), 1.29 (d, 3H, *J* = 7.2 Hz, $ArCH(C\underline{H}_3)$), 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: 403.2280. Optical rotation $[\alpha]_D^{20}$ = +39.3 (c = 1.0, $CHCl_3$).

(*R*)-(2-Methoxy-4-(methoxymethoxy)-5-(3-methylbut-3-en-2-yl)phenylmethanol (11)

A solution of (*R*)-*tert*-butyl(2-methoxy-4-(methoxymethoxy)-5-(3-methylbut-3-en-2-yl)benzyloxy)dimethylsilane (**10**) (120 mg, 0.32 mmol) in THF (6 mL) was treated with *tetra-n*-butylammonium fluoride (250 mg, 0.95 mmol) at 0°C. After stirring for 3 h at 0°C, the resulting mixture was diluted with saturated aqueous NH_4Cl solution (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (25 mL), 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 **11** (107 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, $ArOC\underline{H}_2OCH_3$), 4.84 (d, 2H, *J* = 4.2 Hz, $C(=C\underline{H}_2)CH_3$), 4.60 (d, 2H, *J* = 4.2 Hz, $ArC\underline{H}_2OTBS$), 3.85 (s, 3H, $ArOCH_3$), 3.49 (s, 3H, $ArOCH_2OC\underline{H}_3$), 3.76 (q, 1H, *J* = 7.2 Hz, $ArC\underline{H}(CH_3)$), 1.63 (s, 3H, $C(=CH_2)C\underline{H}_3$), 1.28 (d, 3H, *J* = 6.9 Hz, $ArCH(C\underline{H}_3)$). ^{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: 289.1415. Optical rotation $[\alpha]_D^{20}$ = +58.0 (*c* = 1.0, $CHCl_3$).

(*R*)-2-Methoxy-4-(methoxymethoxy)-5-(3-methylbut-3-en-2-yl)benzaldehyde (2)

To a stirring solution of (*R*)-(2-methoxy-4-(methoxymethoxy)-5-(3-methylbut-3-en-2-yl)phenylmethanol (**11**)

(36 mg, 0.14 mmol) in dry CH_2Cl_2 (3 mL) at 0°C was added Dess-Martin periodinane (160 mg, 0.4 mmol) slowly. After 3 h, the mixture was taken up in water (10 mL) and the aqueous layer was extracted with Et_2O (4 × 10 mL). The combined organic layers were washed with brine (30 mL), 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 **2** (32 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, ArOC$\underline{H}_2$OCH$_3$), 4.84 (d, 2H, *J* = 9.9 Hz, C(=C$\underline{H}_2$)CH$_3$), 3.91 (s, 3H, ArOCH$_3$), 3.74 (q, 1H, *J* = 7.5 Hz, ArC$\underline{H}$(CH$_3$)), 3.49 (s, 3H, ArOCH$_2$OC$\underline{H}_3$), 1.62 (s, 3H, C(=CH$_2$)C$\underline{H}_3$), 1.31 (d, 3H, *J* = 7.2 Hz, ArCH(C$\underline{H}_3$)). ^{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: 287.1260. Optical rotation $[\alpha]^{20}_D$ = +58.2 (*c* = 1.0, $CHCl_3$).

(*E*)-3-(2-Methoxy-4-(methoxymethoxy)-5-((*R*)-3-methylbut-3-en-2-yl)phenyl)-1-(4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl)prop-2-en-1-one (13)

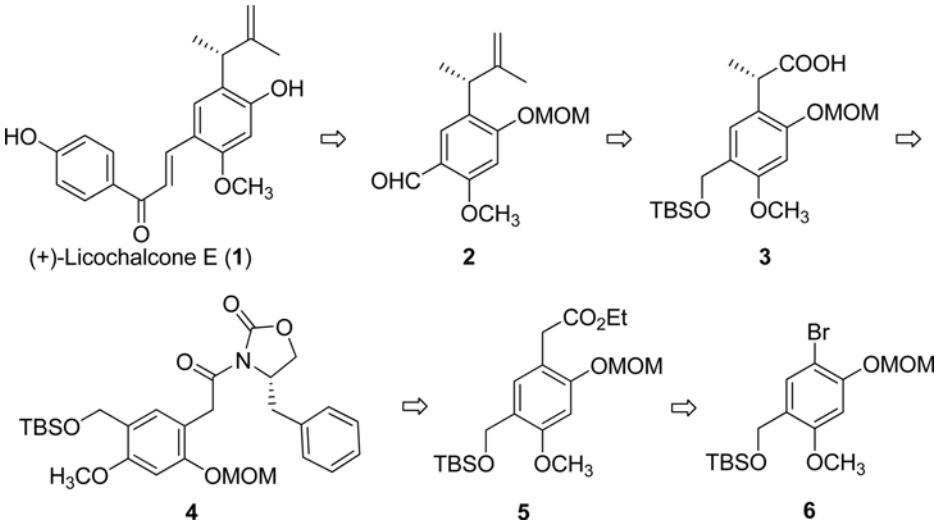
To a solution of (*R*)-2-methoxy-4-(methoxymethoxy)-5-(3-methylbut-3-en-2-yl)-benzaldehyde (**2**) (16 mg, 0.06 mmol) and 1-(4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl) ethanone (**12**) (28 mg, 0.12 mmol) in EtOH and H_2O (2.4 mL, v/v 2:1) at room temperature was added dropwise a solution of KOH (56 mg, 1 mmol) in H_2O (1 mL). The reaction mixture was stirred at room temperature for 48 h and the resulting mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL), 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 **13** (19 mg, 68%) as a yellow power. m.p. 76-78°C. R*f* = 0.45 (3:1 v/v hexanes-EtOAc). ^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.01 (dd, 3H, *J* = 8.7, 15.9 Hz, H2', H6', Hβ), 7.53 (d, 1H, *J* = 15.9 Hz, Hα), 7.38 (s, 1H, H6), 7.12 (d, 2H, *J* = 9.0 Hz, H-3', H-5'), 6.71 (s, 1H, H3), 5.53 (t, 1H, *J* = 3 Hz, THP), 5.25 (s, 2H, ArOC$\underline{H}_2$OCH$_3$), 4.88 (d, 2H, *J* = 8.7 Hz, C(=C$\underline{H}_2$)CH$_3$), 3.90 (s, 3H, ArOCH$_3$), 3.57-3.88 (m, 3H, THP, ArC$\underline{H}$(CH$_3$)), 3.50 (s, 3H, ArOCH$_2$OC$\underline{H}_3$), 1.68-1.92 (m, 6H, THP), 1.57 (s, 3H, C(=CH$_2$)C$\underline{H}_3$), 1.33 (d, 3H, *J* = 7.2 Hz, ArCH(C$\underline{H}_3$)). ^{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: 489.2249. Optical rotation $[\alpha]^{20}_D$ = +42.8 (*c* = 1.0, $CHCl_3$).

(*R*)-Licochalcone E (1)

To a solution of (*E*)-3-(2-methoxy-4-(methoxymethoxy)-5-((*R*)-3-methylbut-3-en-2-yl)-phenyl)-1-(4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl)prop-2-en-1-one (**13**) (10 mg, 0.02 mmol) in dry MeOH (3 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 (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), 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 (*R*)-licochalcone E (**1**) (5.8 mg, 67%) as a yellow power. m.p. 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, Hβ), 7.97 (d, 2H, *J* = 9.0 Hz, H-2', H-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', H-5'), 6.61 (s, 1H, H3), 4.89 (d, 2H, *J* = 7.2 Hz, C(=C$\underline{H}_2$)CH$_3$), 3.88 (s, 3H, ArOCH$_3$), 3.79 (m, 1H, ArC$\underline{H}$(CH$_3$)), 1.67 (s, 3H, C(=CH$_2$)C$\underline{H}_3$), 1.34 (d, 3H, *J* = 7.2 Hz, ArCH(C$\underline{H}_3$)). ^{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 $C_{21}H_{22}O_4Na$ [M+Na]$^+$: 361.1416, found: 361.1421. Optical rotation $[\alpha]^{20}_D$ = +13.6 (*c* = 0.3, acetone).

RESULTS AND DISCUSSION

As shown in Scheme 1, Claisen-Schmidt condensation of the aldehyde **2** with protected 4-hydroxyacetophenone would provide (+)-licochalcone E (**1**) after deprotection. Fully functionalized aldehyde **2** could be prepared by oxidation of the corresponding benzylic alcohol. Conversion of the carboxylic acid in **3** to isopropenyl group in **2** could be done by Weinreb's amide formation then the methyl Grignard reaction followed by the Wittig reaction. The chiral methyl group in **3** could be introduced by the well-established asymmetric alkylation of the aryl acetamide **4** derived from Evans' (*S*)-4-benzyl-2-oxazolidinone. And the aryl acetamide **4** would come from aryl acetate **5** (Ghosh and Gong,

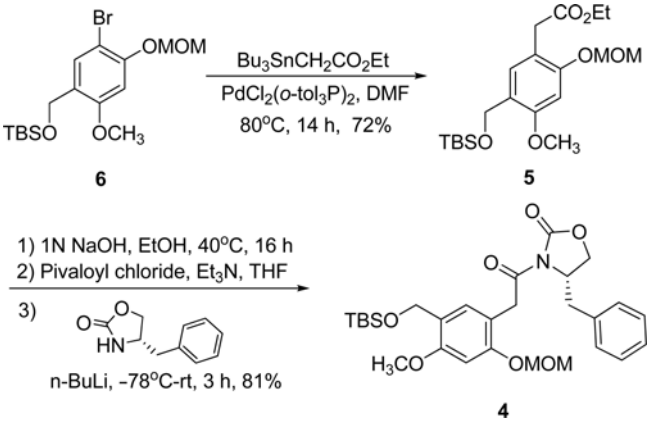


Scheme 1. Retrosynthesis of (+)-licochalcone E (**1**)

2004). Compound **5**, in turn, would be formed from the known aryl bromide **6**, applying the palladium-catalyzed Negishi-Reformatsky coupling reaction with ethyl 2-(tributylstannyl)acetate. Negishi reported the improvement of palladium-catalyzed Reformatsky arylation using organotin analog of Reformatsky reagent in the presence of zinc bromide and catalytic amount of dichlorobis(tri-*o*-tolylphosphine)palladium (Kosugi et al., 1985; Heckrodt and Mulzer, 2003).

Actual synthesis of **4** is depicted in Scheme 2. Palladium-catalyzed Negishi-Reformatsky coupling of [5-bromo-2-methoxy-4-(methoxymethoxy)benzyloxy](*tert*-butyl)dimethylsilane, **6** with ethyl 2-(tributylstannyl) acetate in the presence of dry $ZnBr_2$ and DMF at 80°C afforded 72% yield of aryl acetate **5**. The aryl acetate **5** was hydrolyzed with 1*N*-NaOH in ethanol at 40°C to give aryl acetic acid, which was subsequently converted to the aryl acetamide **4** via the mixed anhydride. Thus, treatment of the arylacetic acid with pivaloyl chloride in the presence of triethylamine gave the mixed anhydride, which was treated with the lithium anion of (*S*)-4-benzyl-2-oxazolidinone to afford the aryl acetamide **4** in 81% overall yield over 3 steps.

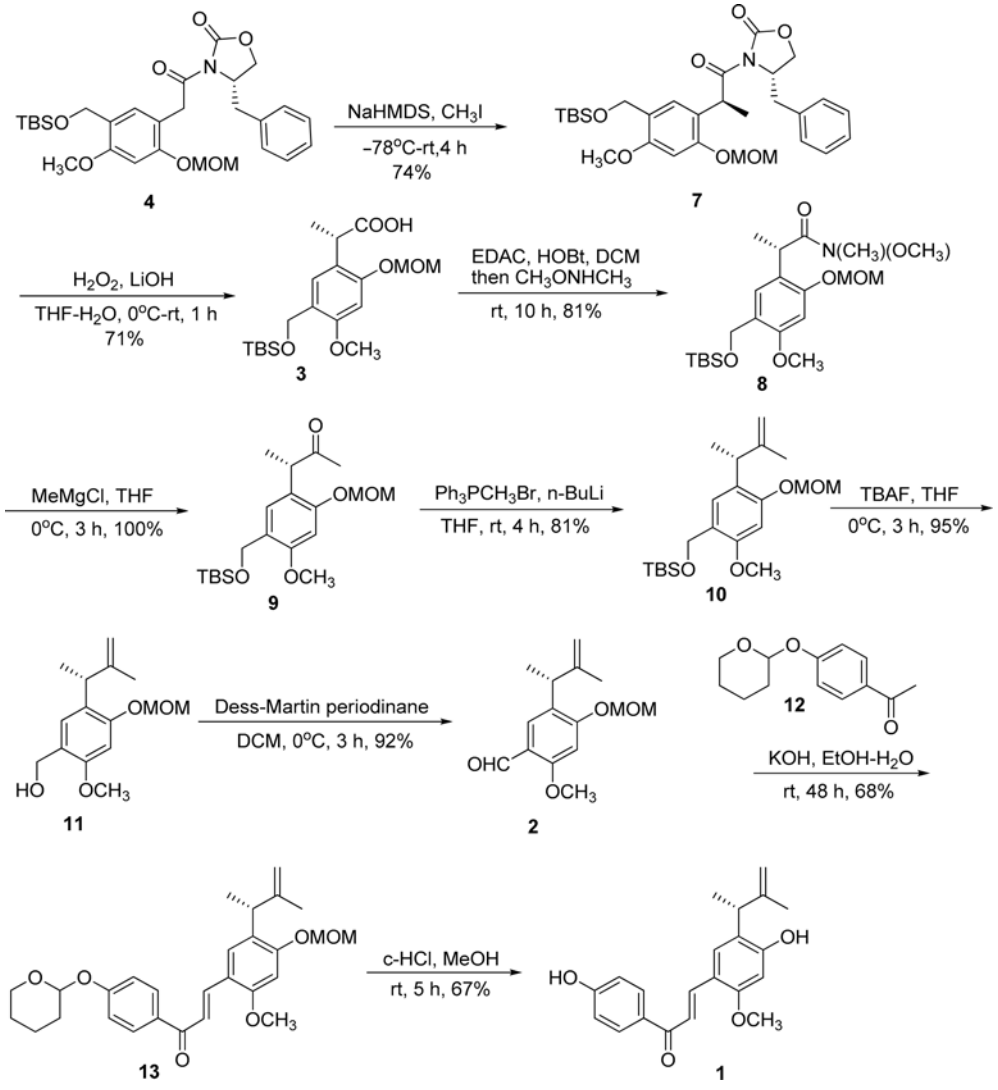
(*S*)-4-Benzyl-2-oxazolidinone-derived compound **4** was treated with NaHMDS and methyl iodide at −78 °C to afford methylated aryl acetamide **7** in 74% yield as shown in Scheme 3. Hydrolysis of the Evans' oxazolidinone in **7** with LiOH and H_2O_2 in THF-H_2O provided (*S*)-2-arylpropionic acid **3** in 71% yield (Qin et al., 2007). The acid **3** was converted to (*R*)-2-aryl-3-methyl-3-butene **10** in 3 steps. Treatment of the (*S*)-2-arylpropionic acid **3** with EDAC, HOBt, followed by *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of triethylamine gave the Weinreb's amide **8**



Scheme 2. Synthesis of key intermediate **4** from **6**

in 81% yield, which was reacted with methyl magnesium chloride in THF at 0°C to furnish the methyl ketone **9** in quantitative yield. This methyl ketone **9** underwent the Wittig reaction with methyltriphenylphosphonium bromide in the presence of *n*-BuLi in THF at ambient temperature to afford (*R*)-2-aryl-3-methyl-3-butene **10** in 81% yield, which was treated with TBAF at 0°C for three hours to give the alcohol **11** in 95% yield.

Oxidation of the benzylalcohol **11** with Dess-Martin periodinane provided the key benzaldehyde **2** in 92% yield. Claisen-Schmidt condensation between the aldehyde **2** and tetrahydropyran-protected 4-hydroxyacetophenone **12** in ethanolic KOH solution furnished protected (+)-licochalcone E (**13**), which was deprotected with *c*-HCl in methanol at room temperature for five hours to give (+)-licochalcone E (**1**) in 46% overall yield in 2 steps. NMR, MS, and IR data of (+)-



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

licochalcone E (**1**) were fully consistent with those for the natural (–)-licochalcone E except optical rotation. (+)-Licochalcone E (**1**) has optical rotation of $[\alpha]_D^{25}$ = +13.6° (*c* = 0.3, acetone) while that of natural (–)-licochalcone was reported as $[\alpha]_D$ = –10.0° (*c* = 0.2, acetone) (Yoon et al., 2005). Thus, we have synthesized the enantiomer of natural (–)-licochalcone E through a stereochemically unambiguous route in 13 steps with 8% overall yield.

We have accomplished for the first time the synthesis of (+)-licochalcone E (**1**) in 13 steps from aryl bromide (**6**) with 8% overall yield. The highlight of this concise asymmetric synthesis of **1** is Palladium-catalyzed Negishi-Reformatsky coupling reaction to form substituted arylacetate and chiral auxiliary-mediated alkylation to control the absolute stereochemistry. We believe this strategy could be used to synthesize other licochalcones for biological evaluation.

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