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Catalytic asymmetric hetero-Diels–Alder route to a key intermediate for the synthesis of calyxin L

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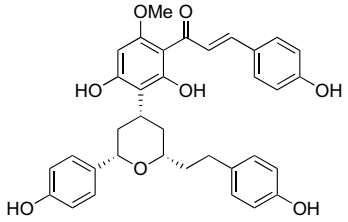
Abstract—A catalytic asymmetric formal synthesis of diarylheptanoid natural product calyxin L has been achieved by incorporating an enantio- and diastereoselective hetero-Diels–Alder (HDA) reaction, a Suzuki–Miyaura coupling, and a stereocontrolled catalytic hydrogenation of 2,4,6-trisubstituted dihydropyran as the key steps. The HDA reaction between 4-(4-benzyloxyphenyl)-2-triethylsilyloxy-1,3-butadiene and (4-benzenesulfonyloxyphenyl)propynal catalyzed by dirhodium(II) tetrakis[(*R*)-3-(benzene-fused-phthalimido)-2-piperidinonate], Rh_2(*R*-BPTPI)$_4$, provided *cis*-2,6-disubstituted tetrahydropyran-4-one in 91% yield with 91% ee.

1. Introduction

Calyxins, recently isolated from the seeds of *Alpinia blepharocalyx* by Kadota et al.,[1] comprise a novel class of diarylheptanoid natural products containing a tetrahydropyran ring. Several members of the calyxin family have been shown to exhibit significant antiproliferative activity against human fibrosarcoma HT-1080 and murine colon 26-L5 carcinoma cells.[1f] Owing to their potential for the development of antitumor agents, this unique class of diarylheptanoids has emerged as highly attractive and important targets for chemical synthesis.[2–4] Rychnovsky et al. recently achieved an asymmetric total synthesis of the proposed structure of epicalyxin F, which is the most active member of the calyxin family, by developing a tandem Prins cyclization and Friedel–Crafts arylation strategy.[4] However, the spectral data for their synthetic material did not match those reported for epicalyxin F and did match those of another natural product isolated from the same plant, calyxin L **1**. We have recently reported the asymmetric synthesis of diarylheptanoid natural products (−)-centrolobine and (−)-de-*O*-methylcentrolobine via a highly enantio- and diastereoselective hetero-Diels–Alder (HDA) reaction between 4-aryl-2-silyloxy-1,3-butadienes **3** and phenylpropargyl aldehyde derivative **4a** catalyzed by dirhodium(II) tetrakis[(*R*)-3-(benzene-fused-phthalimido)-2-piperidinonate], Rh_2(*R*-BPTPI)$_4$ **2** (Eq. 1).[5] As an extension of our study in this field, we herein report an asymmetric formal synthesis of calyxin L **1** exploiting the Rh_2(*R*-BPTPI)$_4$-catalyzed HDA methodology.[6,7]



calyxin L **1**
(proposed structure of epicalyxin F)

2. Results and discussion

Since the highly efficient conversion of **6** to **1** had already been established by Rychnovsky et al.,[4] we directed our efforts to the asymmetric synthesis of the key intermediate **6** (Scheme 1). We envisaged that all-*cis*-2,4,6-trisubstituted tetrahydropyran **6** would be formed through the Suzuki–Miyaura coupling[8] of enol triflate **7** with 2,4,6-trialkoxyphenylboronic acid **8**, followed by catalytic hydrogenation in a stereocontrolled manner. For this type of Suzuki–Miyaura coupling, Mead and Cakir recently reported the coupling of enol triflates derived from β-ketolactones with 2,4,6-trialkoxyphenylboronic acids.[3d] However, to the best of our knowledge, no examples of a Suzuki–Miyaura coupling of enol triflates derived from tetrahydro-

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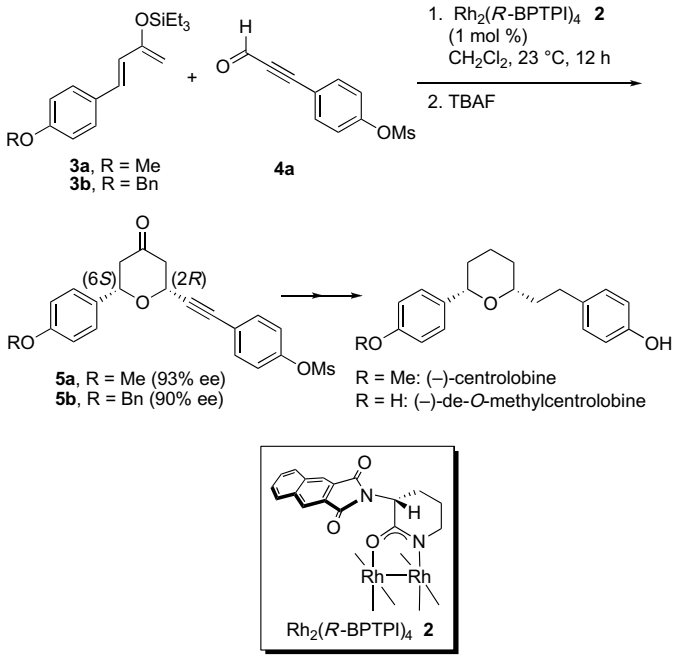


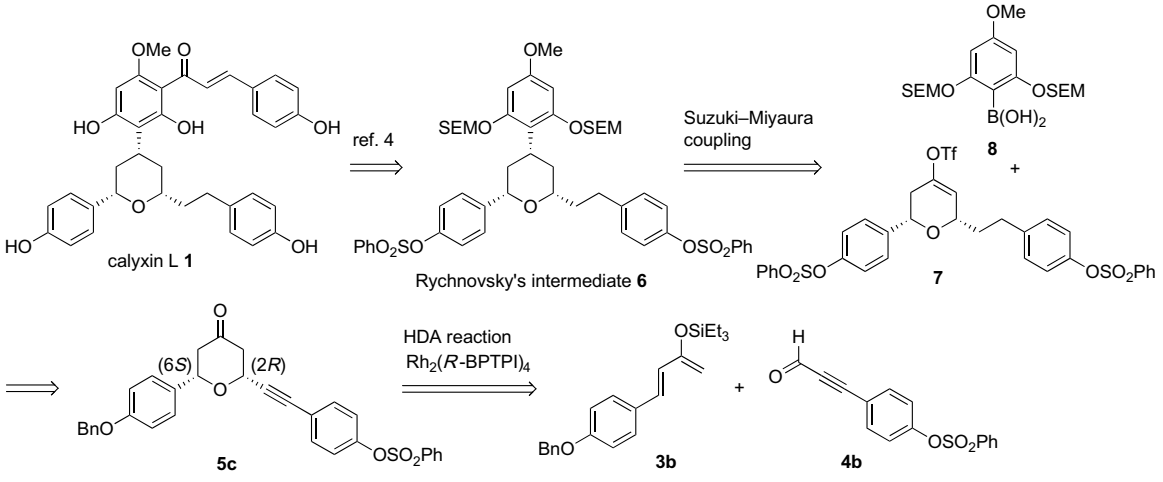
(1)

pyran-4-ones with 2,4,6-trialkoxyphenylboronic acids have been reported.[9] On the basis of our previous work,[5] the *cis*-2,6-disubstituted tetrahydropyran-4-one **5c** could arise from Rh_2(*R*-BPTPI)$_4$-catalyzed HDA reaction between the monooxygenated diene **3b** bearing an electron-rich aromatic ring at C4 and the less sterically demanding and electron-deficient phenylpropargyl aldehyde **4b**.

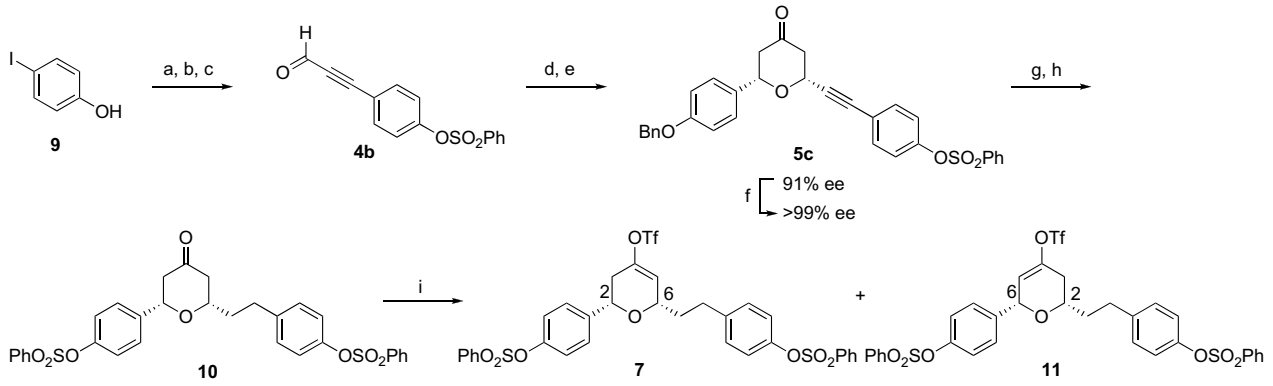
Toward this end, the enol triflate **7** was prepared from 4-iodophenol **9** (Scheme 2). The three-step sequence of the sulfonylation of **9**, Sonogashira coupling[10] with propargyl alcohol, and Dess–Martin oxidation furnished (4-benzenesulfonyloxyphenyl)propynal **4b** in 87% overall yield. The Rh_2(*R*-BPTPI)$_4$-catalyzed HDA reaction of 4-(4-bezyloxyphenyl)-2-triethylsilyloxy-1,3-butadiene **3b**[5] with aldehyde **4b** proceeded smoothly and, after desilylation with TBAF, gave *cis*-2,6-disubstituted tetrahydropyran-4-one **5c** in 91% yield with 91% ee. Enantiomerically pure **5c** [mp 53.5–54.0 °C, $[\alpha]_D^{22} = -2.9$ (*c* 1.00, $CHCl_3$)] was easily obtained by a single recrystallization from benzene–ethanol. Sequential catalytic hydrogenation of the triple bond and hydrogenolysis of the benzyl ether in a single flask was followed by protection of the phenolic hydroxy group as its benzenesulfonate to furnish tetrahydropyran-4-one **10** in 88% yield. Treatment of ketone **10** with NaHMDS at −78 °C followed by the addition of $PhNTf_2$ furnished a 2:1 mixture of enol triflates **7** and **11** in 93% combined yield.[11] The assignment was possible by the analysis of the ^{1}H and COSY NMR spectra of the mixtures, showing two sets of peaks for H-2 (4.64 ppm for **7**, 3.71 ppm for **11**) and H-6 (4.39 ppm for **7**, 5.15 ppm for **11**).

We next prepared 2,4,6-trialkoxyphenylboronic acid **8** from 2-bromo-5-methoxyresorcinol **12**[12] (Scheme 3). Protection of the two phenolic hydroxy groups in **12** with SEMCl under standard conditions afforded **13** in 85% yield. Transmetallation of bromide **13** with *n*-butyllithium followed by sequential treatment with trimethyl borate and aqueous 10% HCl gave arylboronic acid **8** in 70% yield.

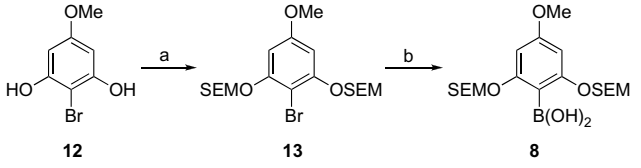
With an inconsequential mixture of enol triflates **7** and **11** and arylboronic acid **8** in hand, the stage was now set for the elaboration of Rychnovsky's intermediate **6** (Scheme 4). Suzuki–Miyaura coupling of enol triflates **7** and **11** with arylboronic acid **8** under standard conditions proceeded smoothly to afford 2,4,6-trisubstituted dihydropyrans **14** and **15** in 86% combined yield with a ratio similar to that of the starting enol triflates. This represents the first example of a Suzuki–Miyaura coupling of enol triflates derived from tetrahydropyran-4-ones with 2,4,6-trialkoxyphenylboronic acids. Catalytic hydrogenation of dihydropyrans **14** and **15** under Mead conditions[3d] pro-



Scheme 1. Retrosynthetic analysis of calyxin L. SEM = 2-(trimethylsilyl)ethoxymethyl.

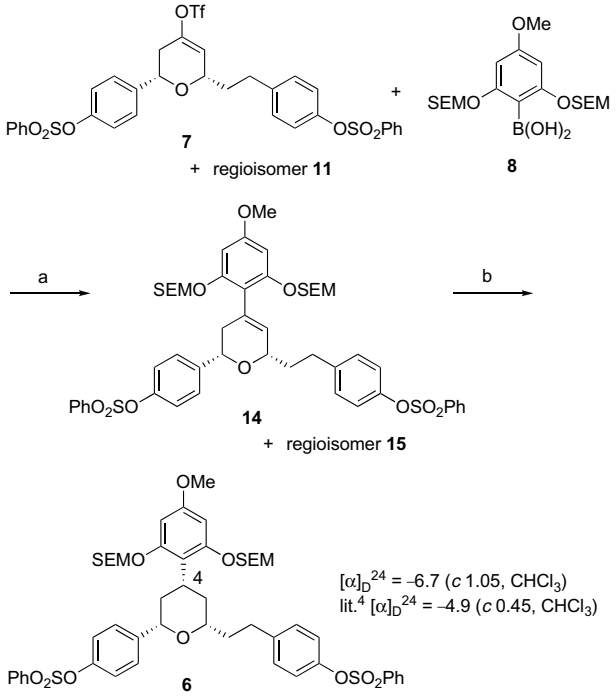


Scheme 2. Reagents and conditions: (a) $PhSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 1 h; (b) propargyl alcohol, $PdCl_2(PPh_3)_2$ (0.5 mol %), CuI (1 mol %), Et_3N, 23 °C, 2 h; (c) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 5 h, 87% (over three steps); (d) Rh_2(*R*-BPTPI)$_4$ **2** (1 mol %), **3b** (1.5 equiv), CH_2Cl_2, 23 °C, 12 h; (e) TBAF, THF, 0.5 h, 91% (over two steps); (f) recrystallization from benzene–EtOH (1:1), 73%; (g) H_2, 10% Pd/C, EtOAc, 5 h; (h) $PhSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 1 h, 88% (over three steps); (i) NaHMDS, THF, −78 °C, 1 h, then $PhNTf_2$, −78 °C, 1 h, and 23 °C, 2 h, 93%, (**7**/**11** = 2:1).



Scheme 3. Reagents and conditions: (a) SEMCl, (*i*-Pr)$_2$NEt, CH_2Cl_2, 23 °C, 0.5 h, 85%; (b) *n*-BuLi, THF, −78 °C, 0.5 h, then $B(OMe)_3$, 23 °C, 12 h, then 10% aq. HCl, 23 °C, 5 min, 70%.

ceeded from the less-hindered face of the molecule to give Rychnovsky's intermediate **6** as the sole product in 89% yield. The spectroscopic data and the specific rotation of the synthetic material **6** {$[\alpha]_D^{24} = -6.7$ (*c* 1.05, $CHCl_3$); lit.[4] $[\alpha]_D^{24} = -4.9$ (*c* 0.45, $CHCl_3$)} were in good agreement with those reported by Rychnovsky et al.[4]



Scheme 4. Reagents and conditions: (a) $PdCl_2(PPh_3)_2$ (5 mol %), THF, 2 M K_2CO_3, reflux, 0.5 h, 86%, (**14**/**15** = 2:1); (b) H_2, 10% Pd/C, EtOAc–EtOH (1:1), 23 °C, 2 h, 89%.

3. Conclusion

We have developed a new and efficient method for the catalytic asymmetric synthesis of calyxin L. The present catalytic method provides easy access to optically active all-*cis*-2,4,6-trisubstituted tetrahydropyrans. Further application of this methodology to the catalytic asymmetric synthesis of other diarylheptanoid natural products is currently in progress.

4. Experimental

4.1. General

Melting points were determined on a Büchi 535 digital melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-5300 spectrometer and absorbance bands are reported in wavenumber (cm^{-1}). ^1H NMR spectra were recorded on JEOL JNM-EX 270 (270 MHz) spectrometer, JEOL JNM-AL 400 (400 MHz) spectrometer or JEOL JNM-ECA 500 (500 MHz) spectrometer. Chemical shifts are reported relative to the internal standard (tetramethylsilane; δ_H 0.00, $CDCl_3$; δ_H 7.26 or C_6D_6; δ_H 7.20). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, and integration. ^{13}C NMR spectra were recorded on JEOL JNM-AL 400 (100 MHz) or JEOL JNM-ECA 500 (125 MHz) spectrometer. The following internal references were used ($CDCl_3$; δ 77.0 or C_6D_6; δ 128.0). Optical rotations were measured on a JASCO P-1030 digital polarimeter at the sodium D line (589 nm). EI-MS spectra were obtained on a JEOL JMS-FABmate spectrometer, operating with ionization energy of 70 eV. FAB-MS spectra were obtained on a JEOL JMS-HX 110 spectrometer. Column chromatography was

carried out on Kanto Silica Gel 60 N (63–210 mesh) or Wakogel® C-200 (75–150 μm). Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates with visualization by UV light, anisaldehyde stain solution or phosphomolybdic acid stain solution. Analytical high performance liquid chromatography (HPLC) was performed on a JASCO PU-1580 intelligent HPLC pump with JASCO UV-1575 intelligent UV/vis detector. Detection was performed at 254 nm. A Chiralpak AD-H column (0.46 cm × 25 cm) from Daicel was used. Retention times (t_R) and peak ratios were determined with JASCO-Borwin analysis system.

All non-aqueous reactions were carried out in flame-dried glassware under an argon atmosphere unless otherwise noted. Reagents and solvents were purified by standard means. Dehydrated CH_2Cl_2 and THF were purchased from Kanto Chemical Co., Inc. Compound Rh_2(*R*-BPTPI)$_4$·$3H_2O$ **2** was prepared from D-ornithine according to the literature procedure.[6]

4.2. Preparation of enol triflates 7 and 11

4.2.1. (4-Benzenesulfonyloxyphenyl)propynal 4b. To a solution of 4-iodophenol **9** (4.4 g, 20 mmol) and Et_3N (5.6 mL, 40 mmol) in CH_2Cl_2 (30 mL) was added benzenesulfonyl chloride (3.7 g, 21 mmol) at 0 °C. After stirring at this temperature for 1 h, the reaction was quenched with one piece of ice and diluted with water (10 mL). The whole was extracted with EtOAc (100 mL), and the organic layer was washed with water (20 mL) and brine (2 × 20 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel, 9:1 hexane/EtOAc) provided 4-iodophenyl benzenesulfonate (7.13 g, 99%) as a colorless oil; TLC $R_f = 0.21$ (9:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.71–6.76 (m, 2H, *Ar*), 7.52–7.63 (m, 4H, *Ar*), 7.66–7.72 (m, 1H, *Ar*), 7.81–7.86 (m, 2H, *Ar*). To a stirred mixture of 4-iodophenyl benzenesulfonate (6.1 g, 17 mmol), copper iodide (32 mg, 0.17 mmol, 1 mol %), $PdCl_2(PPh_3)_2$ (60 mg, 0.085 mmol, 0.5 mol %), and propargyl alcohol (2.0 mL, 34 mmol) was added Et_3N (15 mL) at 0 °C. After stirring at 23 °C for 2 h, the reaction mixture was diluted with EtOAc (40 mL), and filtered through a plug of Celite with EtOAc (20 mL). Filtration and evaporation in vacuo followed by column chromatography (silica gel, 2:1 hexane/EtOAc) provided 4-(3-hydroxy-1-propynyl)phenyl benzenesulfonate (4.49 g, 92%) as a pale yellow solid; mp 57.5–58.0 °C; TLC $R_f = 0.29$ (1:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.67 (t, 1H, $J = 6.2$ Hz, O*H*), 4.48 (d, 2H, $J = 6.2$ Hz, CH_2OH), 6.91–6.96 (m, 2H, *Ar*), 7.32–7.38 (m, 2H, *Ar*), 7.50–7.56 (m, 2H, *Ar*), 7.65–7.71 (m, 1H, *Ar*), 7.81–7.84 (m, 2H, *Ar*). To a solution of 4-(3-hydroxy-1-propynyl)phenyl benzenesulfonate (1.3 g, 5.0 mmol) in CH_2Cl_2 (20 mL) was added Dess–Martin periodinane (2.3 g, 5.5 mmol) at 0 °C. After stirring at this temperature for 5 h, the mixture was poured into an ice-cooled solution of saturated aqueous $NaHCO_3$ (10 mL) containing $Na_2S_2O_3$·H_2O (1.0 g). The whole was extracted with EtOAc (60 mL). The organic layer was washed with water (2 × 10 mL) and brine (2 × 10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel, 4:1 hexane/EtOAc) provided **4b** (1.36 g, 95%) as a yellow oil; TLC $R_f = 0.38$ (2:1 hexane/EtOAc); IR (film) 2242, 2192, 1661, 1378, 1203, 1182, 1157 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.03–7.08 (m, 2H, *Ar*), 7.52–7.59 (m, 4H, *Ar*), 7.68–7.74 (m, 1H, *Ar*), 7.83–7.87 (m, 2H, *Ar*), 9.40 (s, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.7 (C), 92.8 (C), 118.2 (C), 122.7 (CH), 128.1 (CH), 129.1 (CH), 134.4 (CH), 134.5 (CH), 134.6 (C), 151.0 (C), 176.3 (C=O); HRMS (EI): $(M)^+$ calcd for $C_{15}H_{10}O_4S$, 286.0300; found, 286.0296; Anal. Calcd for $C_{15}H_{10}O_4S$: C, 62.93; H, 3.52; S, 11.20. Found: C, 62.65; H, 3.62; S, 11.27.

4.2.2. (2*R*,6*S*)-2-(4-Benzenesulfonyloxyphenylethynyl)-6-(4-benzyloxyphenyl)tetrahydropyran-4-one 5c. To a solution of (4-benzenesulfonyloxyphenyl)propynal **4b** (570 mg, 2.0 mmol) in CH_2Cl_2 (2 mL) was added Rh_2(*R*-BPTPI)$_4$·$3H_2O$ **2** (29 mg, 0.02 mmol, 1 mol %). The color of the solution changed from pale yellow to brown. After stirring for 5 min, a solution of *trans*-4-(4-benzyloxyphenyl)-2-triethylsilyloxy-1,3-butadiene **3b**[5] (1.1 g, 3.0 mmol) in CH_2Cl_2 (2 mL) was added at 23 °C. After stirring at this temperature for 12 h, the reaction mixture turned into a deep green solution. The whole mixture was concentrated in vacuo to furnish the crude product (1.7 g) as a green oil, which was purified by column chromatography (Wakogel® C-200, 4:1 hexane/EtOAc with 2% Et_3N) to give silylenol ether (1.2 g) as a colorless oil. To a solution of the silylenol ether in THF (4 mL) was added a solution of TBAF in THF (1.0 M, 2.0 mL, 2.0 mmol) at 23 °C. After stirring at this temperature for 0.5 h, the mixture was poured into a two-layer mixture of EtOAc (20 mL) and water (10 mL), and the whole was extracted with EtOAc (40 mL). The organic layer was washed with water (10 mL) and brine (2 × 10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (1.1 g) as a pale yellow oil, which was purified by column chromatography (silica gel, 2:1 hexane/EtOAc) to give **5c** (980 mg, 91%) as a pale yellow solid; mp 52.0–53.0 °C; TLC $R_f = 0.28$ (2:1 hexane/EtOAc); $[\alpha]_D^{21} = -2.5$ (*c* 1.00, $CHCl_3$) for 91% ee; IR (KBr) 2235, 1722, 1377, 1200, 1177, 1152 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60–2.88 (m, 4H, CH_2COCH_2), 4.64 (dd, $J = 2.8$, 11.5 Hz, 1H, C6-*H*), 4.74 (dd, $J = 3.2$, 11.5 Hz, 1H, C2-*H*), 5.07 (s, 2H, PhCH_2O), 6.91–6.99 (m, 4H, *Ar*), 7.31–7.43 (m, 9H, *Ar*), 7.50–7.54 (m, 2H, *Ar*), 7.65–7.69 (m, 1H, *Ar*), 7.79–7.82 (m, 2H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.4 (CH_2), 48.8 (CH_2), 67.3 (CH), 69.8 (CH_2), 78.3 (CH), 84.8 (C), 87.2 (C), 114.8 (CH), 120.9 (C), 122.2 (CH), 127.17 (CH), 127.23 (CH), 127.8 (CH), 128.2 (CH), 128.3 (CH), 129.0 (CH), 132.0 (C), 133.0 (CH), 134.2 (CH), 134.7 (C), 136.5 (C), 149.2 (C), 158.5 (C), 204.1 (C=O); HRMS (EI): $(M)^+$ calcd for $C_{32}H_{26}O_6S$, 538.1450; found, 538.1445; Anal. Calcd for $C_{32}H_{26}O_6S$: C, 71.36; H, 4.87; S, 5.95. Found: C, 71.23; H, 4.88; S, 6.04. The enantiomeric excess of **5c** was determined to be 91% by HPLC with a Chiralpak AD-H column (1:1 hexane/*i*-PrOH, 1.0 mL/min); t_R (major) = 22.2 min for (2*R*,6*S*)-enantiomer; t_R (minor) = 34.8 min for (2*S*,6*R*)-enantiomer. The preferred absolute stereochemistry was established as (2*R*,6*S*) by the transformation of **5c** into **6** (vide infra).

Recrystallization was performed by dissolving **5c** (980 mg, 1.8 mmol, 91% ee) in 3 mL of hot benzene after which were added 2 mL of EtOH. The pale yellow needles formed at room temperature after standing overnight, and were collected by suction, washed with 1 mL of ice cold benzene–EtOH (1:1) and dried in vacuo to give enantiomerically pure **5c** (715 mg, 73%); mp 53.5–54.0 °C; $[\alpha]_D^{22} = -2.9$ (*c* 1.00, $CHCl_3$). The enantiopurity of **5c** was determined to be >99% ee by the comparison of HPLC retention time with the racemic sample.

4.2.3. (2*S*,6*S*)-2-(4-Benzenesulfonyloxyphenyl)-6-[2-(4-benzenesulfonyloxyphenyl)ethyl]tetrahydropyran-4-one 10. To a solution of **5c** (270 mg, 0.50 mmol, >99% ee) in EtOAc (10 mL) was added 10% Pd/C (30 mg), and the resulting mixture was stirred under hydrogen at atmospheric pressure at 23 °C for 5 h. The reaction mixture was then filtered through a plug of Celite, and the Celite filter cake was washed with EtOAc (10 mL). The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 3:2 hexane/EtOAc) to afford (2*S*,6*S*)-6-[2-(4-benzenesulfonyloxyphenyl)ethyl]-2-(4-hydroxyphenyl)-tetrahydropyran-4-one (215 mg, 95%) as a white amorphous solid; TLC $R_f = 0.23$ (1:1 hexane/EtOAc); $[\alpha]_D^{21} = -52.6$ (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79–1.88 (m, 1H, CH_2CHHCH), 1.97–2.06 (m, 1H, CH_2CHHCH), 2.34–2.45 (m, 2H, $COCH_2$), 2.52–2.63 (m, 2H, $COCH_2$), 2.67–2.85 (m, 2H, CH_2CH_2CH), 3.64–3.70 (m, 1H, C6-*H*), 4.52 (dd, $J = 3.6$, 10.5 Hz, 1H, C2-*H*), 5.16 (s, 1H, O*H*), 6.83–6.89 (m, 4H, *Ar*), 7.06–7.09 (m, 2H, *Ar*), 7.22–7.27 (m, 2H, *Ar*), 7.50–7.54 (m, 2H, *Ar*), 7.64–7.68 (m, 1H, *Ar*), 7.81–7.84 (m, 2H, *Ar*). To a solution of (2*S*,6*S*)-6-[2-(4-benzenesulfonyloxyphenyl)-ethyl]-2-(4-hydroxyphenyl)tetrahydropyran-4-one (200 mg, 0.43 mmol) and Et_3N (0.18 mL, 1.3 mmol) in CH_2Cl_2 (4 mL) was added benzenesulfonyl chloride (110 mg, 0.65 mmol) at 0 °C. After stirring at this temperature for 1 h, the reaction was quenched by the addition of crushed ice. The whole was extracted with EtOAc (30 mL). The organic layer was washed with water (2 × 5 mL) and brine (2 × 5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel, 3:2 hexane/EtOAc) provided **10** (238 mg, 93%) as a white amorphous solid; TLC $R_f = 0.21$ (1:1 hexane/EtOAc); $[\alpha]_D^{21} = -45.5$ (*c* 1.00, $CHCl_3$); IR (KBr) 2227, 1714, 1371, 1199, 1177, 1151 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82–1.89 (m, 1H, CH_2CHHCH), 1.98–2.07 (m, 1H, CH_2CHHCH), 2.32–2.49 (m, 3H, $CHHCOCH_2$), 2.59–2.62 (m, 1H, $CHHCOCH_2$), 2.67–2.74 (m, 1H, $CHHCH_2CH$), 2.78–2.85 (m, 1H, $CHHCH_2CH$), 3.65–3.71 (m, 1H, C6-*H*), 4.57 (dd, $J = 2.6$, 11.7 Hz, 1H, C2-*H*), 6.86–6.90 (m, 2H, *Ar*), 6.99–7.03 (m, 2H, *Ar*), 7.06–7.09 (m, 2H, *Ar*), 7.28–7.31 (m, 2H, *Ar*), 7.51–7.57 (m, 4H, *Ar*), 7.64–7.71 (m, 2H, *Ar*), 7.82–7.88 (m, 4H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.7 (CH_2), 37.4 (CH_2), 47.3 (CH_2), 49.1 (CH_2), 75.9 (CH), 77.4 (CH), 122.0 (CH), 122.3 (CH), 126.6 (CH), 128.2 (CH), 128.9 (CH), 129.0 (CH), 129.3 (CH), 134.0 (CH), 134.1 (CH), 135.1 (C), 139.7 (C), 140.3 (C), 147.5 (C), 148.7 (C), 205.5 (C=O); HRMS (EI): $(M)^+$ calcd for $C_{31}H_{28}O_8S_2$ 592.1225, found 592.1230; Anal. Calcd for $C_{31}H_{28}O_8S_2$: C, 62.82; H, 4.76; S, 10.82. Found: C, 62.74; H, 4.72; S, 10.89.

4.2.4. (2*S*,6*S*)-2-(4-Benzenesulfonyloxyphenyl)-6-[2-(4-benzenesulfonyloxyphenyl)ethyl]-3,6-dihydro-2*H*-pyran-4-yl trifluoromethanesulfonate 7 and (2*S*,6*S*)-6-(4-benzenesulfonyloxyphenyl)-2-[2-(4-benzenesulfonyloxyphenyl)ethyl]-3,6-dihydro-2*H*-pyran-4-yl trifluoromethanesulfonate 11. To a 1.0 M solution of NaHMDS in THF (0.41 mL, 0.41 mmol) was added a solution of **10** (220 mg, 0.37 mmol) in THF (4 mL) at −78 °C. After stirring at this temperature for 1 h, a solution of $PhNTf_2$ (160 mg, 0.44 mmol) in THF (1 mL) was added. After stirring at this temperature for 1 h, the reaction mixture was allowed to warm to 23 °C and stirred for 2 h. The mixture was poured into saturated aqueous NH_4Cl (5 mL), and the whole was extracted with EtOAc (30 mL). The organic layer was washed with water (5 mL) and brine (2 × 5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel, 2:1 hexane/EtOAc) provided an inseparable mixture of **7** and **11** (238 mg, 93%) as a white amorphous solid; *TLC $R_f = 0.30$ (2:1 hexane/EtOAc); *$[\alpha]_D^{22} = -41.8$ (*c* 1.00, $CHCl_3$); *IR (KBr) 1376, 1200, 1179, 1152 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, data for **7**) δ 1.80–2.00 (m, 2H, CH_2CH_2CH), 2.44–2.60 (m, 2H, C3-*H*), 2.64–2.81 (m, 2H, CH_2CH_2CH), 4.39 (br, 1H, C6-*H*), 4.64 (dd, $J = 4.0$, 9.6 Hz, 1H, C2–*H*), 5.79 (s, 1H, C5-*H*), 6.87–6.90 (m, 2H, *Ar*), 6.99–7.01 (m, 2H, *Ar*), 7.06–7.10 (m, 2H, *Ar*), 7.25–7.29 (m, 2H, *Ar*), 7.50–7.57 (m, 4H, *Ar*), 7.65–7.71 (m, 2H, *Ar*), 7.82–7.87 (m, 4H, *Ar*); ^{1}H NMR (400 MHz, $CDCl_3$, data for **11**) δ 1.80–2.00 (m, 2H, CH_2CH_2CH), 2.27–2.32 (m, 1H, C3-*H*), 2.44–2.60 (m, 1H, C3–*H*), 2.64–2.81 (m, 2H, CH_2CH_2CH), 3.71 (m, 1H, C2–*H*), 5.15 (br, 1H, C6–*H*), 5.79 (s, 1H, C5–*H*), 6.87–6.90 (m, 2H, *Ar*), 6.99–7.01 (m, 2H, *Ar*), 7.06–7.10 (m, 2H, *Ar*), 7.25–7.29 (m, 2H, *Ar*), 7.50–7.57 (m, 4H, *Ar*), 7.65–7.71 (m, 2H, *Ar*), 7.82–7.87 (m, 4H, *Ar*); *^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2 (CH_2), 30.6 (CH_2), 33.7 (CH_2), 35.7 (CH_2), 36.2 (CH_2), 36.4 (CH_2), 72.9 (CH), 73.6 (CH), 74.8 (CH), 75.4 (CH), 116.7 (C), 119.9 (CH), 120.1 (CH), 122.10 (CH), 122.13 (CH), 122.4 (CH), 122.5 (CH), 123.3 (C), 126.8 (CH), 127.1 (C), 128.3 (CH), 128.4 (CH), 129.0 (CH), 129.1 (CH), 129.36 (CH), 129.43 (CH), 134.1 (CH), 134.2 (CH), 135.1 (C), 135.2 (C), 138.0 (C), 139.3 (C), 140.2 (C), 140.4 (C), 145.8 (C), 146.3 (C), 147.6 (C), 148.9 (C), 149.3 (C); *HRMS (EI): $(M)^+$ calcd for $C_{32}H_{27}F_3O_{10}S_3$, 724.0718; found 724.0713 (*data for mixed triflates **7** and **11**).

4.3. Preparation of arylboronic acid 8

4.3.1. 2-Bromo-5-methoxy-1,3-bis-[2-(trimethylsilyl)ethoxymethoxy]benzene 13. To a solution of 2-bromo-5-methoxyresorcinol **12**[12] (220 mg, 1.0 mmol) and $(i\text{-Pr})_2NEt$ (570 mg, 4.4 mmol) in CH_2Cl_2 (5 mL) was added 2-(trimethylsilyl)ethoxymethyl chloride (370 mg, 2.2 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After stirring at 23 °C for 0.5 h, the reaction was quenched with saturated $NaHCO_3$ solution (2 mL), and the whole was extracted with EtOAc (30 mL). The organic layer was washed with water (5 mL) and brine (2 × 5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by

column chromatography (silica gel, 19:1 hexane/EtOAc) provided **13** (408 mg, 85%) as a colorless oil; TLC $R_f = 0.31$ (9:1 hexane/EtOAc);IR (film) 1249, 1043 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ −0.01 (s, 18H, $Si(CH_3)_3$), 0.91–0.98 (m, 4H, $CH_2CH_2Si(CH_3)_3$), 3.76 (s, 3H, OCH_3), 3.79 (m, 4H, $CH_2CH_2Si(CH_3)_3$), 5.25 (s, 4H, OCH_2O), 6.47 (s, 2H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.4 (CH_3), 18.0 (CH_2), 55.5 (CH_3), 66.6 (CH_2), 93.5 (CH_2), 94.7 (C), 96.2 (CH), 155.3 (C), 159.9 (C); HRMS (EI): $(M)^+$ calcd for $C_{19}H_{35}BrO_5Si_2$, 478.1206; found, 478.1208; Anal. Calcd for $C_{19}H_{35}BrO_5Si_2$: C, 47.59; H, 7.36; Br; 16.66. Found: C, 47.52; H, 7.17; Br, 16.64.

4.3.2. 4-Methoxy-2,6-bis-[2-(trimethylsilyl)ethoxymethoxy]-phenylboronic acid 8. To a solution of **13** (390 mg, 0.82 mmol) in THF (5 mL) was added 1.59 M solution of *n*-BuLi in hexane (0.57 mL, 0.90 mmol) at −78 °C. The mixture was stirred at −78 °C for 0.5 h, and trimethyl borate (0.18 mL, 1.6 mmol) was added. The mixture was allowed to warm to 23 °C and stirring was continued for an additional 12 h. The mixture was acidified with 10% HCl and stirred for 5 min. The whole was extracted with EtOAc (2 × 15 mL), and the combined organic layers were washed with water (5 mL) and brine (2 × 5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel, 9:1 hexane/EtOAc) provided **8** (256 mg, 70%) as a colorless oil; TLC $R_f = 0.22$ (4:1 hexane/EtOAc); ^1H NMR (270 MHz, C_6D_6) δ −0.06 (s, 18H, $Si(CH_3)_3$), 0.81 (t, $J = 8.2$ Hz, 4H, $CH_2CH_2Si(CH_3)_3$), 3.38 (s, 3H, OCH_3), 3.54 (t, $J = 8.2$ Hz, 4H, $CH_2CH_2Si(CH_3)_3$), 4.78 (s, 2H, OCH_2O), 6.60 (s, 2H, *Ar*), 7.50 (s, 2H, $B(OH)_2$); ^{13}C NMR (100 MHz, C_6D_6) δ −1.3 (CH_3), 18.1 (CH_2), 55.0 (CH), 67.0 (CH_2), 93.4 (CH_2), 95.4 (CH), 163.8 (C), 165.1 (C).

4.4. Synthesis of Rychnovsky's intermediate 6

4.4.1. (2*S*,6*S*)-2-(4-Benzenesulfonyloxyphenyl)-6-[2-(4-benzenesulfonyloxyphenyl)ethyl]-4-{4-methoxy-2,6-bis-[2-(trimethylsilyl)ethoxymethoxy]phenyl}-3,6-dihydro-2*H*-pyran 14 and (2*S*,6*S*)-6-(4-benzenesulfonyloxyphenyl)-2-[2-(4-benzenesulfonyloxyphenyl)ethyl]-4-{4-methoxy-2,6-bis-[2-(trimethylsilyl)-ethoxymethoxy]phenyl}-3,6-dihydro-2*H*-pyran 15. To a mixture of **7** and **11** (190 mg, 0.27 mmol) in THF (6 mL) was added **8** (140 mg, 0.32 mmol), $PdCl_2(PPh_3)_2$ (9.3 mg, 0.013 mmol, 5 mol %) and 2 M K_2CO_3 (2.1 mL, 4.2 mmol), and the mixture was refluxed for 0.5 h. After cooling, the reaction mixture was extracted with EtOAc (30 mL), and the organic layer was washed with water (5 mL) and brine (2 × 5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel, 3:1 hexane/EtOAc) provided an inseparable mixture of **14** and **15** (182 mg, 86%) as a white amorphous solid; *TLC $R_f = 0.20$ (3:1 hexane/EtOAc); *$[\alpha]_D^{23} = -11.8$ (*c* 1.01, $CHCl_3$); *IR (KBr) 1902, 1606, 1376, 1200, 1178, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ for **14**) δ −0.05 (s, 18H, $Si(CH_3)_3$), 0.89–0.94 (m, 4H, $CH_2CH_2Si(CH_3)_3$), 1.73–2.01 (m, 2H, CH_2CH_2CH), 2.15–2.45 (m, 2H, C3-*H*), 2.65–2.89 (m, 2H, CH_2CH_2CH), 3.65–3.71 (m, 4H, $CH_2CH_2Si(CH_3)_3$), 3.78 (s, 3H, OCH_3), 4.48 (br, 1H, C6–*H*), 5.15 (s, 4H, OCH_2O), 5.53 (s, 1H, C5–*H*), 6.39 (s, 2H, *Ar*), 6.85–6.88 (m, 2H, *Ar*), 6.93–6.97 (m, 2H, *Ar*), 7.08–7.13 (m, 2H, *Ar*), 7.28–7.39 (m, 2H, *Ar*), 7.50–7.55 (m, 4H, *Ar*), 7.64–7.68 (m, 2H, *Ar*), 7.81–7.86 (m, 4H, *Ar*); ^1H NMR (400 MHz, $CDCl_3$ for **15**) δ −0.03 (s, 18H, $Si(CH_3)_3$), 0.89–0.94 (m, 4H, $CH_2CH_2Si(CH_3)_3$), 1.73–2.01 (m, 2H, CH_2CH_2CH), 2.15–2.45 (m, 2H, C3-*H*), 2.65–2.89 (m, 2H, CH_2CH_2CH), 3.65–3.71 (m, 5H, $CH_2CH_2Si(CH_3)_3$ and C2–*H*), 3.77 (s, 3H, OCH_3), 5.12 (s, 4H, OCH_2O), 5.20 (br, 1H, C6–*H*), 5.52 (s, 1H, C5–*H*), 6.39 (s, 2H, *Ar*), 6.85–6.88 (m, 2H, *Ar*), 6.93–6.97 (m, 2H, *Ar*), 7.08–7.13 (m, 2H, *Ar*), 7.28–7.39 (m, 2H, *Ar*), 7.50–7.55 (m, 4H, *Ar*), 7.64–7.68 (m, 2H, *Ar*), 7.81–7.86 (m, 4H, *Ar*); *^{13}C NMR (100 MHz, $CDCl_3$) δ −1.44 (CH_3), −1.40 (CH_3), 17.88 (CH_2), 17.91 (CH_2), 30.3 (CH_2), 31.0 (CH_2), 34.8 (CH_2), 36.9 (CH_2), 37.0 (CH_2), 37.1 (CH_2), 55.3 (CH_3), 66.10 (CH_2), 66.14 (CH_2), 73.6 (CH), 74.5 (CH), 74.8 (CH), 77.0 (CH), 92.9 (CH_2), 94.8 (CH), 113.8 (C), 113.9 (C), 121.9 (CH), 122.0 (CH), 126.7 (CH), 128.0 (CH), 128.23 (CH), 128.25 (CH), 128.6 (CH), 128.89 (CH), 128.93 (CH), 128.95 (CH), 129.3 (CH), 129.4 (CH), 129.7 (C), 130.0 (C), 133.9 (CH), 134.0 (CH), 135.1 (C), 135.18 (C), 135.24 (C), 135.3 (C), 140.8 (C), 141.1 (C), 141.5 (C), 141.8 (C), 147.32 (C), 147.34 (C), 148.3 (C), 148.7 (C), 155.6 (C), 159.69 (C), 159.72 (C); *HRMS (FAB): $(M+Na)^+$ calcd for $C_{50}H_{62}O_{12}S_2Si_2Na$, 997.3119; found, 997.3124; *Anal. Calcd for $C_{50}H_{62}O_{12}S_2Si_2$: C, 61.57; H, 6.41; S, 6.58. Found: C, 61.29; H, 6.28; S, 6.55 (*data for mixed dihydropyrans **14** and **15**).

4.4.2. (2*S*,4*R*,6*S*)-2-(4-Benzenesulfonyloxyphenyl)-6-[2-(4-benzenesulfonyloxyphenyl)ethyl]-4-{4-methoxy-2,6-bis-[2-(trimethylsilyl)ethoxymethoxy]phenyl}tetrahydropyran 6.[4] To a mixture of **14** and **15** (50 mg, 0.05 mmol) in EtOAc (2 mL)–EtOH (2 mL) was added 10% Pd/C (10 mg), and the resulting mixture was stirred under hydrogen at an atmospheric pressure at 23 °C for 2 h. The reaction mixture was then filtered through a plug of Celite, and the Celite filter cake was washed with EtOAc (5 mL). The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 4:1 hexane/EtOAc) to afford **6** (44.6 mg, 89%) as a white amorphous solid; TLC $R_f = 0.39$ (2:1 hexane/EtOAc); $[\alpha]_D^{24} = -6.7$ (*c* 1.05, $CHCl_3$) {lit.,[4] $[\alpha]_D^{24} = -4.9$ (*c* 0.45, $CHCl_3$)}; IR (film) 2952, 2923, 1607, 1589, 1376, 1152 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.03 (s, 18H, $Si(CH_3)_3$), 0.92–0.96 (m, 4H, $CH_2CH_2Si(CH_3)_3$), 1.51 (d, $J = 12.6$ Hz, 1H, C5–*H*), 1.73–1.77 (m, 1H, C3–*H*), 1.88–1.95 (m, 1H, CH_2CHHCH), 1.88–1.95 (m, 1H, CH_2CHHCH), 2.06–2.15 (m, 1H, C5–*H*), 2.18–2.27 (m, 1H, C3–*H*), 2.65–2.73 (m, 1H, $CHHCH_2CH$), 2.75–2.83 (m, 1H, $CHHCH_2CH$), 3.50–3.61 (m, 2H, C4–*H* and C6–*H*), 3.69–3.73 (m, 4H, $CH_2CH_2Si(CH_3)_3$), 3.75 (s, 3H, CH_3), 4.41 (d, $J = 9.8$ Hz, 1H, C2-*H*), 5.19 (s, 4H, OCH_2O), 6.40 (s, 2H, *Ar*), 6.85–6.88 (m, 2H, *Ar*), 6.91–6.94 (m, 2H, *Ar*), 7.06–7.09 (m, 2H, *Ar*), 7.29–7.32 (m, 2H, *Ar*), 7.50–7.54 (m, 4H, *Ar*), 7.64–7.68 (m, 2H, *Ar*), 7.82–7.85 (m, 4H, *Ar*); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.34 (CH_3), 18.1 (CH_2), 31.2 (CH_2), 32.4 (CH), 35.1 (CH_2), 36.8 (CH_2), 37.8 (CH_2), 55.3 (CH_3), 66.3 (CH_2), 77.5 (CH), 78.8 (CH), 93.0 (CH_2), 94.9 (CH), 114.2 (CH), 121.9 (CH), 122.0 (CH), 126.9 (CH), 128.4 (CH), 128.97 (CH), 129.00 (CH), 129.5 (CH), 134.0 (C), 135.36 (C), 135.40 (C),

141.4 (C), 142.3 (C), 147.4 (C), 148.3 (C), 156.7 (C), 159.0 (C); HRMS (FAB): $(M+Na)^+$ calcd for $C_{50}H_{64}O_{12}S_2Si_2Na$, 999.3275; found, 999.3283. The synthetic material **6** was identical in all respects with the reported spectral data (IR, ^1H NMR, ^{13}C NMR, HRMS).

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References

1. (a) Prasain, J. K.; Li, J.-X.; Tezuka, Y.; Tanaka, K.; Basnet, P.; Dong, H.; Namba, T.; Kadota, S. *J. Nat. Prod.* **1998**, *61*, 212–216; (b) Gewali, M. B.; Tezuka, Y.; Banskota, A. H.; Ali, M. S.; Saiki, I.; Dong, H.; Kadota, S. *Org. Lett.* **1999**, *1*, 1733–1736; (c) Tezuka, Y.; Ali, M. S.; Banskota, A. H.; Kadota, S. *Tetrahedron Lett.* **2000**, *41*, 5903–5907; (d) Tezuka, Y.; Gewali, M. B.; Ali, M. S.; Banskota, A. H.; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 208–213; (e) Ali, M. S.; Tezuka, Y.; Banskota, A. H.; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 491–496; (f) Ali, M. S.; Banskota, A. H.; Tezuka, Y.; Saiki, I.; Kadota, S. *Biol. Pharm. Bull.* **2001**, *24*, 525–528.
2. For total synthesis of (−)-blepharocalyxin D, see: (a) Ko, H. M.; Lee, D. G.; Kim, M. A.; Kim, H. J.; Park, J.; Lah, M. S.; Lee, E. *Org. Lett.* **2007**, *9*, 141–144; (b) Ko, H. M.; Lee, D. G.; Kim, M. A.; Kim, H. J.; Park, J.; Lah, M. S.; Lee, E. *Tetrahedron* **2007**, *63*, 5797–5805.
3. For synthetic studies of calyxins, see: (a) Li, W.; Mead, K. T.; Smith, L. T. *Tetrahedron Lett.* **2003**, *44*, 6351–6353; (b) Cakir, S. P.; Mead, K. T. *J. Org. Chem.* **2004**, *69*, 2203–2205; (c) Yang, X.-F.; Wang, M.; Zhang, Y.; Li, C.-J. *Synlett* **2005**, 1912–1916; (d) Cakir, S. P.; Mead, K. T. *Tetrahedron Lett.* **2006**, *47*, 2451–2454.
4. For total synthesis and structure revision of calyxins F, G, L, and M and epicalyxins G and M, see: Tian, X.; Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 3176–3183.
5. Washio, T.; Yamaguchi, R.; Abe, T.; Nambu, H.; Anada, M.; Hashimoto, S. *Tetrahedron* **2007**, *63*, 12037–12046.
6. Anada, M.; Washio, T.; Shimada, N.; Kitagaki, S.; Nakajima, M.; Shiro, M.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 2665–2668.
7. Doyle and co-workers were the first to demonstrate that chiral dirhodium(II) carboxamidates are highly efficient Lewis acid catalysts for enantioselective HDA reactions between Danishefsky's diene and aldehydes: (a) Doyle, M. P.; Phillips, I. M.; Hu, W. *J. Am. Chem. Soc.* **2001**, *123*, 5366–5367; (b) Doyle, M. P.; Valenzuela, M.; Huang, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5391–5395; (c) Valenzuela, M.; Doyle, M. P.; Hedberg, C.; Hu, W.; Holmstrom, A. *Synlett* **2004**, 2425–2428.
8. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Miyaura, N. In *Cross-Coupling Reactions*; Miyaura, N., Ed.; Topics in Current Chemistry; Springer: Berlin, 2002; Vol. 219, pp 11–59.
9. Suzuki–Miyaura coupling of aliphatic ketone-derived enol triflates with 2,4,6-trialkoxyphenylboronic acids has not yet been reported. In this context, Carreño et al. recently reported the Suzuki–Miyaura coupling of an enol triflate derived from 7-methoxy-1-tetralone with 2,4,6-trimethoxyphenylboronic acid: (a) Carreño, M. C.; González-López, M.; Latorre, A.; Urbano, A. *Synlett* **2005**, 1601–1605; (b) Carreño, M. C.; González-López, M.; Latorre, A.; Urbano, A. *J. Org. Chem.* **2006**, *71*, 4956–4964.
10. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470.
11. McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979–982.
12. Kiehlmann, E.; Lauener, R. W. *Can. J. Chem.* **1989**, *67*, 335–344.