Highly Stereoselective Prins Cyclization of *Z* and *E* γ -Brominated Homoallylic Alcohols to 2,4,5,6-Tetrasubstituted Tetrahydropyrans

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Supplementary Material

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General Methods

Experiments involving moisture and/or air sensitive components were performed in oven-dried glassware. Commercial solvents and reagents were used without further purification with the following exceptions: Hexane, dichloromethane, ethyl acetate and diethyl ether were fractionally distilled. Aldehydes were distilled before used. Analytical thin layer chromatography (TLC) was performed using Merck 60 F₂₅₄ precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. Proton nuclear magnetic resonance spectra (¹H NMR) were recorded on a Bruker Avance DPX 300 and Bruker AMX 400 & 500 spectrophotometers (CDCl₃ as solvent). Chemical shifts for ¹H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe₄ (δ 0.0) and relative to the signal of chloroform-d (δ 7.2700, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); qu (quintet); dd (doublets of doublet); ddd (doublets of doublets of doublet); dt (doublets of triplet); td (triplets of doublet) or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (¹³C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe₄ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). High Resolution Mass (**HRMS**) spectra were obtained using Finnigan MAT95XP GC/HRMS (Thermo Electron Corporation). Mass spectral data were reported in units of mass to charge (m/z) and relative intensity (**RI**).

Preparation of (Z)- γ -brominated-homoallylic alcohol (Z)-1.

1. To prepare lithium diisopropylamide (LDA)

To an oven dried round-bottom 50 mL flask equipped with a magnetic stirring bar was added diisopropylamine (10.0 mmol, 1.40 mL), anhydrous tetrahydrofuran (10 mL). The mixture was cooled to 0 °C prior to dropwise addition of *n*-butyl lithium (10.0 mmol, 6.3 mL, 1.6 M in hexane). The mixture was stirred at 0 °C for 30 minutes before being transferred into the other flask.

2. To prepare (Z)- γ -brominated-homoallylic alcohol (Z)-1.

To an oven dried round-bottom 100 mL flask equipped with a magnetic stirring bar was added ZnBr₂ (2.5 mmol, 0.5630 g, 1.25 equiv.), allyl bromide (5.0 mmol, 0.43 mL, 2.5 equiv.) and tetrahydrofuran (20 mL). The mixture was stirred and cooled to -78 °C. The preformed LDA was added dropwise *via* a plastic cannula and the mixture was stirred for around 20 minutes. Hydrocinnamaldehyde (2.0 mmol, 0.26 mL, 1.0 equiv.) was then added.¹ The reaction was allowed to proceed for 3 hours at -78 °C. The reaction was quenched by pouring the reaction mixture into 1 M HCl solution (20 mL). The aqueous layer was extracted with diethyl ether (50 mL $\times$ 3) and the combined organic extracts were washed with water and brine, and dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (10% ether in hexane) to afford (Z)-6-bromo-1-phenylhex-5-en-3-ol (Z)-1 as pale yellowish oil in 62 % yield.²

R_f: 0.45 (hexane : ethyl acetate 4:1)

¹H NMR (300 MHz, CDCl₃) δ 7.28-7.14 (m, 5H), 6.23 (d, *J* = 7.08 Hz, 1H), 6.16 (q, *J* = 6.90 Hz, 1H), 3.72 (qu, *J* = 5.70 Hz, 1H), 2.77 (td, *J* = 7.63, 13.53 Hz, 1H), 2.65 (td, *J* = 7.92, 13.95 Hz, 1H), 2.45-2.33 (m, 2H), 2.15 (s, 1H), 1.81-1.74 (m, 2H).

¹³C NMR (75.4 MHz, CDCl₃) δ 141.6, 130.8, 128.3, 128.2, 125.8, 109.8, 69.8, 38.4, 37.5, 31.8.

FTIR (neat) 3356, 3082, 3061, 3024, 2926, 2860, 1715, 1622, 1603, 1495, 1454, 1314, 1279, 1080, 1053, 1030, 748, 700, 675 cm⁻¹.

HRMS *m/z* Calcd for C₁₂H₁₅BrO : 254.0301, found: 254.0305, **RI**: 100.0;

Calcd for C₁₂H₁₅⁸¹BrO : 256.0280, found: 256.0287, **RI**: 92.5.

Preparation of 1-Phenyl-6-trimethylsilanyl-hex-5-yn-3-ol (**1a**).

Trimethylsilylpropargyl bromide (956 mg, 5.0 mmol, 1.25 equiv.) was added to a suspension of the indium powder (574 mg, 5.0 mmol, 1.25 equiv.) and indium bromide (142 mg, 0.40 mmol, 0.1 equiv.) in 5 mL anhydrous THF at room temperature. After 15 minutes, the hydrocinnamaldehyde (537 mg, 4.0 mmol, 1.0 equiv.) was added at room temperature. The mixture was refluxed overnight, and quenched with 50 mL 1M HCl solution.³ The aqueous layer was extracted with diethyl ether (50 mL $\times$ 3), and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, concentrated *in vacuo*, and purified *via* flash chromatography (20% ethyl acetate in hexane) to afford 1-Phenyl-6-trimethylsilanyl-hex-5-yn-3-ol (**1a**) 592 mg in 60% yield as yellow oil.

R_f: 0.45 (hexane : ethyl acetate 4:1)

¹H NMR (400 MHz, CDCl₃) δ 7.31-7.17 (m, 5H), 3.79-3.72 (m, 1H), 2.81 (td, J = 7.52, 13.72 Hz, 1H), 2.70 (td, J = 8.12, 13.88 Hz, 1H), 2.48 (dd, J = 4.76, 16.80 Hz, 1H), 2.38 (dd, J = 6.88, 16.76 Hz, 1H), 1.99 (d, J = 5.04 Hz, 1H), 1.99-1.84 (m, 2H), 0.16 (s, 9H).

¹³C NMR (100 MHz, CDCl₃) δ 141.7, 128.4, 128.4, 125.9, 102.9, 87.8, 69.0, 37.8, 31.8, 29.0, 0.05.

FTIR (neat) 3356, 3026, 2957, 2174, 1495, 1454, 1418, 1250, 1080, 1030, 841, 760, 698, 648 cm⁻¹.

HRMS m/z Calcd for C₁₅H₂₁OSi [M-H]⁺: 245.1356, found [M-H]⁺: 245.1366.

Preparation of (Z)-1-phenyl-6-trimethylsilanyl-hex-5-en-3-ol (**1b**).

To an oven 50mL dried round-bottom flask equipped with a magnetic stirring bar was added **1a** (1.0 mmol, 24.6 mg, 1.0 equiv.) diluted with 1.5 mL anhydrous diethyl ether and stirred at 0 °C. DIBAL-H in heptane (1.0M in heptane) (2.6 mL, 2.6 mmol, 2.6 equiv.) was slowly added.⁴ The reaction was allowed to proceed at room temperature for 29 hours before quenching with methanol (10 mL) and saturated sodium potassium tartrate solution (10 mL). The aqueous layer was extracted with diethyl

ether (20 mL $\times$ 3) and the combined organic extracts were washed with water and brine, and dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (5.0 % ethyl acetate in hexane) to afford the (Z)-1-phenyl-6-trimethylsilyl-hex-5-en-3-ol (**1b**) as colorless oil in 64 % yield.

R_f: 0.47 (hexane : ethyl acetate 4:1)

¹H NMR (400 MHz, CDCl₃) δ 7.30-7.17 (m, 5H), 6.32 (ddd, J = 7.00, 7.96, 14.32 Hz, 1H), 5.70 (td, J = 1.16, 14.12 Hz, 1H) 3.70-3.67 (m, 1H), 2.82-2.73 (m, 1H), 2.71-2.67 (m, 1H), 2.36-2.30 (m, 1H), 1.83-1.77 (m, 1H), 1.57 (d, J = 4.00 Hz, 1H), 0.13 (s, 9H).

¹³C NMR (100 MHz, CDCl₃) δ 143.9, 141.9, 133.2, 128.41, 128.39, 125.8, 70.5, 41.3, 38.5, 32.0, 0.25.

FTIR (neat) 3354, 3339, 2954, 2897, 1604, 1497, 1454, 1408, 1248, 1078, 1053, 858, 830, 764, 698 cm⁻¹.

HRMS m/z Calcd for C₁₅H₂₄OSi : 248.1591, found : 248.1595.

Preparation of (*E*)- γ -brominated-homoallylic alcohol (*E*)-1.

To an oven dried 50 mL round-bottom flask equipped with a magnetic stirring bar was added (Z)-1-phenyl-6-trimethylsilyl-hex-5-en-3-ol (**1b**) (1126.9 mg, 5.11 mmol, 1.0 equiv.) diluted with 15 mL anhydrous dichloromethane, and cooled to -78 °C, stirred. Bromine (0.26 mL, 5.11 mmol, 1.0 equiv.) was added dropwise into the solution of **1b**. The reaction was quenched by adding 10% Na₂SO₃ solution upon the persistence of brownish color.⁵ The reaction mixture was extracted with dichloromethane (50 mL $\times$ 3) and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered. The filtrate was cooled to -20 °C prior to addition of TBAF (10.22 mL, 10.22 mmol, 2.0 equiv.). The mixture was allowed to be stirred at -20 °C for 30 minutes. The reaction mixture was concentrated in vacuo. The residual crude was purified *via* flash chromatography (20% ethyl acetate in hexane) to afford (*E*)-1 as yellow oil in 90% yield.

R_f: 0.34 (hexane : ethyl acetate 4:1)

¹H NMR (400 MHz, CDCl₃) δ 7.30-7.18 (m, 5H), 6.20 (td, J = 7.36, 13.60 Hz, 1H), 6.12 (d, J = 13.60 Hz) 3.68-3.65 (m, 1H), 2.79 (td, J = 8.12, 13.39 Hz, 1H), 2.66 (td, J = 8.26, 13.96 Hz, 1H), 2.29-2.22 (m, 1H), 2.17 (td, J = 7.49, 14.13 Hz, 1H), 1.79-1.73 (m, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 141.6, 133.9, 128.41, 128.36, 125.9, 106.9, 69.7, 40.8, 38.3, 31.9.

FTIR (neat) 3377, 3360, 3026, 2931, 2860, 1620, 1499, 1454, 1433, 1275, 1242, 1084, 1051, 943, 748, 700 cm^{-1} .

HRMS m/z Calcd for $\text{C}_{12}\text{H}_{15}\text{BrO}$: 254.0301, found : 254.0292, **RI**: 100.0;
Calcd for $\text{C}_{12}\text{H}_{15}^{81}\text{BrO}$: 256.0280, found : 256.0273, **RI**: 97.1.

General Procedures for the construction of 2,4,5,6-tetrasubstituted -2,6-crossed-4,5-dibromo-tetrahydropyrans.

To an oven-dried 25mL round-bottom flask equipped with a magnetic stirring bar was added indium bromide (106.0 mg, 0.30 mmol, 1.0 equiv.) and anhydrous dichloromethane (1.5 mL). The mixture was allowed to cool to 0 °C with vigorous stirring. (Z)- γ -brominated-homoallylic alcohol (**Z**)-**1** (91.8 mg, 0.36 mmol, 1.2 equiv.) in 1 mL dry CH_2Cl_2 was introduced into the suspension, and 5 minutes later bromotrimethylsilane TMSBr (0.05 mL, 0.36 mmol, 1.2 equiv.) was added. Cyclohexanecarboxaldehyde (33.7 mg, 0.30 mmol, 1.0 equiv.) in 1 mL dry CH_2Cl_2 was slowly introduced over 10 minutes. The reaction was allowed to proceed at 0 °C for 90 minutes before quenching with saturated sodium bicarbonate solution (5 mL). The aqueous layer was extracted with diethyl ether (10 mL $\times$ 3) and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (diethyl ether vs. hexane 0.5%) to afford **2a** as a white solid in 95 % yield.

m.p. 70.5-71.1 °C; **R_f**: 0.69 (hexane : diethyl ether 4:1)

^1H NMR (300 MHz, CDCl_3) δ 7.29-7.14 (m, 5H), 4.38 (d, J = 2.79 Hz, 1H), 4.22 (ddd, J = 3.12, 3.93, 12.19 Hz, 1H), 3.32-3.23 (m, 1H), 2.85-2.76 (m, 2H), 2.69 (td, J = 8.10, 13.75 Hz, 1H), 2.23-2.15 (m, 2H), 1.97-1.87 (m, 2H), 1.77-1.66 (m, 6H), 1.31-1.13 (m, 3H), 0.98 (m, 1H), 0.79 (m, 1H).

^{13}C NMR (75.4 MHz, CDCl_3) δ 141.5, 128.5, 128.3, 125.9, 83.8, 77.0, 59.5, 50.2, 41.5, 38.3, 36.9, 31.4, 29.9, 27.4, 26.3, 25.6, 25.5.

FTIR (KBr) 3021, 2930, 2918, 2851, 1450, 1433, 1313, 1224, 1080, 1067, 1055, 744, 696, 575 cm^{-1} .

HRMS m/z Calcd for $\text{C}_{19}\text{H}_{26}\text{Br}_2\text{O}$: 428.0345, found : 428.0332, **RI**:51.6;

Calcd for C₁₉H₂₆⁸¹Br₂O : 432.0304, found : 432.0294, **RI**: 50.5.

Crystal structure of **2a**.

Table 1. Crystal data and structure refinement for **2a**.

Empirical formula	C ₁₉ H ₂₆ Br ₂ O		
Formula weight	430.22		
Temperature	273(2) K		
Wavelength	0.71073 Å		
Crystal system	Monoclinic		
Space group	P2(1)/c		
Unit cell dimensions	a = 10.4511(4) Å	b = 18.9558(7) Å	c = 9.7638(4) Å
			= 90°
			= 105.932(2)°
			= 90°
Volume	1860.00(12) Å ³		
Z	4		
Density (calculated)	1.536 Mg/m ³		
Absorption coefficient	4.359 mm ⁻¹		
F(000)	872		
Crystal size	0.40 x 0.20 x 0.20 mm ³		
Theta range for data collection	2.15 to 30.55°.		
Index ranges	-14<=h<=14, -27<=k<=26, -13<=l<=13		
Reflections collected	23668		
Independent reflections	5664 [R(int) = 0.0272]		
Completeness to theta = 30.55°	99.6 %		
Absorption correction	Semi-empirical from equivalents		

Max. and min. transmission	0.4760 and 0.2745
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	5664 / 0 / 303
Goodness-of-fit on F ²	1.024
Final R indices [I > 2σ(I)]	R1 = 0.0264, wR2 = 0.0553
R indices (all data)	R1 = 0.0426, wR2 = 0.0599
Largest diff. peak and hole	0.541 and -0.335 e.Å ⁻³

Yellow oil; **R_f**: 0.75 (hexane : diethyl ether 4:1)

¹H NMR (400 MHz, CDCl₃) δ 7.29-7.16 (m, 5H), 4.31 (s, 1H), 4.29-4.26 (m, 1H), 3.37-3.31 (m, 1H), 3.22 (dd, *J* = 5.57, 7.27 Hz, 1H), 2.80 (ddd, *J* = 5.48, 8.77, 14.03 Hz, 1H), 2.70 (td, *J* = 8.13, 13.87 Hz, 1H), 2.23 (q, *J* = 11.99 Hz, 1H), 2.00-1.91 (m, 2H), 1.87-1.80 (m, 1H), 1.75-1.51 (m, 1H), 1.58-1.51 (m, 1H), 1.45-1.41 (m, 1H), 1.32-1.28 (m, 11H), 0.88 (t, *J* = 7.21 Hz, 3H).

¹³C NMR (75.4 MHz, CDCl₃) δ 141.5, 128.5, 128.4, 125.9, 79.3, 77.2, 61.8, 49.8, 37.9, 36.8, 35.4, 31.8, 31.4, 29.5, 29.4, 29.2, 25.2, 22.7, 14.1.

FTIR (neat) 2951, 2924, 2855, 1495, 1454, 1114, 1084, 910, 735, 698 cm⁻¹.

HRMS *m/z* Calcd for C₂₁H₃₂Br₂O : 458.0814, found : 458.0802, **RI**: 51.1;
 Calcd for C₂₁H₃₂Br⁸¹BrO : 460.0794, found : 460.0785, **RI**: 100;
 Calcd for C₂₁H₃₂⁸¹Br₂O : 462.0773, found : 462.0767, **RI**: 49.7.

Yellow oil; **R_f**: 0.67 (hexane : diethyl ether 4:1)

¹H NMR (400 MHz, CDCl₃) δ 7.30-7.14 (m, 5H), 4.41 (d, *J* = 2.90 Hz, 1H), 4.27 (td, *J* = 4.01, 12.21 Hz), 3.35-3.29 (m, 1H), 2.99 (d, *J* = 9.96 Hz, 1H), 2.83 (ddd, *J* = 5.22, 8.76, 13.98 Hz, 1H), 2.68 (dt, *J* = 8.11, 13.95 Hz, 1H), 2.23 (q, *J* = 12.45 Hz, 1H), 2.02-1.91 (m, 2H), 1.86-1.78 (m, 2H), 1.76-1.67 (m, 2H), 1.62-1.51 (m, 1H), 1.48-1.39 (m, 1H), 1.28-1.19 (m, 1H), 0.88 (t, t, *J* = 7.34 Hz, 6H).

^{13}C NMR (75.4 MHz, CDCl_3) δ 141.5, 128.5, 128.4, 125.9, 80.9, 77.4, 60.2, 50.3, 43.1, 38.3, 36.9, 31.5, 19.8, 18.9, 9.7, 9.6.

FTIR (neat) 3024, 2961, 2934, 2874, 1495, 1454, 1381, 1290, 1220, 1112, 1082, 746, 698, 600 cm^{-1} .

HRMS m/z Calcd for $\text{C}_{18}\text{H}_{26}\text{Br}^{81}\text{BrO}$: 418.0324, found : 418.0319, **RI**: 100;
Calcd for $\text{C}_{18}\text{H}_{26}^{81}\text{Br}_2\text{O}$: 420.0304, found : 420.0300, **RI**: 50.0.

Pale yellow oil; **R_f**: 0.50 (hexane : diethyl ether 4:1)

^1H NMR (400 MHz, CDCl_3) δ 7.40-7.18 (m, 10H), 4.58 (t, J = 1.48 Hz, 1H), 4.56 (s, 1H), 4.50 (dt, J = 4.12, 11.36 Hz, 1H), 3.63-3.55 (m, 1H), 2.87 (ddd, J = 5.53, 8.99 14.05 Hz, 1H), 2.79 (td, J = 8.15, 13.86 Hz, 1H), 2.38 (q, J = 12.46 Hz, 1H), 2.15-2.02 (m, 2H), 1.92-1.82 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 141.5, 139.5, 128.5, 128.4, 128.2, 127.8, 125.9, 125.4, 79.7, 77.4, 62.4, 49.3, 37.5, 36.9, 31.4.

FTIR (neat) 3061, 3026, 2930, 2855, 2174, 1732, 1602, 1495, 1452, 1418, 1228, 1123, 1088, 1066, 955, 741, 698, 573 cm^{-1} .

HRMS m/z Calcd for $\text{C}_{19}\text{H}_{20}\text{Br}_2\text{O}$: 421.9875, found : 421.9896, **RI**: 54.6;
Calcd for $\text{C}_{19}\text{H}_{20}\text{Br}^{81}\text{BrO}$: 423.9855, found : 423.9845, **RI**: 100.

White solid, m.p. 91.6-92.3 $^{\circ}\text{C}$; **R_f**: 0.67 (hexane : diethyl ether 4:1)

^1H NMR (400 MHz, CDCl_3) δ 7.29-7.16 (m, 10H), 4.22 (s, 1H), 4.17 (td, J = 3.88, 11.84 Hz, 1H), 3.33-3.27 (m, 1H), 3.15 (dd, J = 3.80, 8.40 Hz, 1H), 2.83-2.66 (m, 4H), 2.27-2.16 (m, 2H), 2.00-1.87 (m, 2H), 1.79-1.68 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 141.4, 141.1, 128.43, 128.38, 128.38, 128.34, 126.0, 125.9, 77.7, 77.1, 61.7, 49.5, 37.8, 37.0, 36.7, 31.4, 31.3.

FTIR (KBr) 3024, 2957, 2924, 2852, 1597, 1495, 1452, 1314, 1255, 1220, 1123, 1087, 1026, 935, 743, 696, 602, 511, 482 cm^{-1} .

HRMS m/z Calcd for $\text{C}_{21}\text{H}_{24}\text{Br}_2\text{O}$: 450.0188, found : 450.0193, **RI**: 50.7;

Calcd for $\text{C}_{21}\text{H}_{24}\text{Br}^{81}\text{BrO}$: 452.0168, found : 452.0168, **RI**: 100;

Calcd for $\text{C}_{21}\text{H}_{24}^{81}\text{Br}_2\text{O}$: 454.0147, found : 454.0155, **RI**: 49.1.

Pale yellow oil; **R_f**: 0.81 (hexane : diethyl ether 4:1)

^1H NMR (400 MHz, CDCl_3) δ 7.30-7.15 (m, 5H), 4.15 (ddd, J = 4.92, 10.44, 12.00 Hz, 1H), 3.92 (t, J = 10.28 Hz, 1H), 3.26-3.23 (m, 2H), 2.77 (ddd, J = 5.24, 8.57, 13.80 Hz 1H), 2.67 (td, J = 8.15, 13.74 Hz, 1H), 2.30 (ddd, J = 1.64, 4.92, 13.24 Hz, 1H), 2.01 (s, 1H), 1.95 (q, J = 12.27 Hz, 1H), 1.86-1.77 (m, 3H), 1.70-1.64 (m, 2H), 1.60-1.50 (m, 3H), 1.35-1.13 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3) δ 141.5, 128.4, 128.3, 125.9, 85.1, 76.0, 56.7, 55.0, 44.9, 39.9, 36.7, 31.4, 30.8, 26.6, 26.4, 26.2, 24.4.

FTIR (neat) 3026, 2928, 2853, 1495, 1450, 1161, 1126, 1088, 1057, 1032, 1001, 750, 736, 698, 492 cm^{-1} .

HRMS m/z Calcd for $\text{C}_{19}\text{H}_{26}\text{Br}_2\text{O}$: 428.0345, found : 428.0352, **RI**: 44.9;

Calcd for $\text{C}_{19}\text{H}_{26}\text{Br}^{81}\text{BrO}$: 430.0324, found : 430.0335, **RI**: 100;

Calcd for $\text{C}_{19}\text{H}_{26}^{81}\text{Br}_2\text{O}$: 432.0304, found : 432.0314, **RI**: 48.8.

Pale yellow oil; **R_f**: 0.78 (hexane : diethyl ether 4:1)

^1H NMR (400 MHz, CDCl_3) δ 7.30-7.14 (m, 5H), 4.14 (ddd, J = 4.96, 10.56, 12.08 Hz, 1H), 3.75 (t, J = 10.20 Hz, 1H), 3.39 (dt, J = 2.12, 10.24 Hz, 1H), 3.31-3.24 (m, 1H), 2.75 (ddd, J = 5.25, 8.64, 13.74 Hz, 1H), 2.66 (td, J = 8.18, 13.74 Hz, 1H), 2.32 (ddd, J = 1.40, 4.84, 13.20 Hz, 1H), 2.12-2.07 (m, 1H),

1.99 (q, $J = 12.16$ Hz, 1H), 1.89-1.80 (m, 1H), 1.72-1.64 (m, 1H), 1.72-1.64 (m, 1H), 1.59-1.51 (m, 2H), 1.31-1.29 (m, 11H), 0.90-0.87 (t, $J = 6.96$ Hz, 3H).

^{13}C NMR (75.4 MHz, CDCl_3) δ 141.4, 128.43, 128.41, 125.9, 81.6, 75.9, 59.5, 54.3, 44.9, 36.7, 34.2, 31.9, 31.4, 29.5, 29.3, 29.2, 25.3, 22.7, 14.1.

FTIR (neat) 3356, 3026, 2957, 2174, 1495, 1454, 1418, 1250, 1080, 1030, 841, 760, 698, 648 cm^{-1} .

HRMS m/z Calcd for $\text{C}_{21}\text{H}_{32}\text{Br}^{81}\text{BrO}$: 460.0794, found : 460.0782, **RI**: 100;

Calcd for $\text{C}_{21}\text{H}_{32}^{81}\text{Br}_2\text{O}$: 462.0773, found : 462.0777, **RI**: 51.2.

Pale yellow oil; **R_f**: 0.72 (hexane : diethyl ether 4:1)

^1H NMR (400 MHz, CDCl_3) δ 7.30-7.14 (m, 5H), 4.18 (ddd, $J = 4.92, 10.32, 12.12$ Hz, 1H), 3.98 (t, $J = 10.20$ Hz, 1H), 3.47 (dd, $J = 1.92, 10.12$ Hz, 1H), 3.30-3.23 (m, 1H), 2.77 (ddd, $J = 5.21, 8.90, 13.89$ Hz, 1H), 2.64 (td, $J = 8.25, 13.78$ Hz, 1H), 2.32 (ddd, $J = 1.72, 4.88, 13.24$ Hz, 1H), 1.97 (q, $J = 12.28$ Hz, 1H), 1.88-1.78 (m, 2H), 1.73-1.64 (m, 1H), 1.60-1.38 (m, 3H), 1.32-1.19 (m, 1H), 0.93 (t, $J = 7.47$ Hz, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 141.5, 128.4, 125.9, 82.5, 76.3, 57.3, 55.0, 45.0, 43.1, 36.9, 31.4, 23.2, 20.6, 12.3, 11.9.

FTIR (neat) 3026, 2953, 2924, 2854, 1495, 1454, 1369, 1159, 1130, 1114, 1082, 1053, 748, 735, 698 cm^{-1} .

HRMS m/z Calcd for $\text{C}_{18}\text{H}_{26}\text{Br}^{81}\text{BrO}$: 418.0324, found : 418.0326, **RI**: 100;

Calcd for $\text{C}_{18}\text{H}_{26}^{81}\text{Br}_2\text{O}$: 420.0304, found : 420.0306, **RI**: 47.6.

White solid, m.p. 76.0-77.0 °C; **R_f**: 0.58 (hexane : diethyl ether 4:1)

¹H NMR (400 MHz, CDCl₃) δ 7.39-7.11 (m, 10H), 4.39 (d, *J* = 10.00 Hz, 1H), 4.28 (ddd, *J* = 4.88, 10.72, 11.76 Hz, 1H), 4.05 (t, *J* = 10.20 Hz, 1H), 3.53-3.44 (m, 1H), 2.73-2.63 (m, 2H), 2.48 (ddd, *J* = 1.16, 4.68, 13.36 Hz, 1H), 2.17 (q, *J* = 12.28 Hz, 1H), 1.97-1.88 (m, 1H), 1.81-1.72 (m, 1H).

¹³C NMR (75.4 MHz, CDCl₃) δ 141.2, 138.9, 128.7, 128.4, 128.4, 128.3, 127.7, 125.9, 84.9, 76.7, 59.2, 53.7, 44.4, 36.5, 31.2.

FTIR (KBr) 3055, 3022, 2980, 2931, 2918, 2848, 1495, 1452, 1433, 1364, 1305, 1281, 1215, 1165, 1149, 1076, 1057, 763, 725, 704, 698, 527 cm⁻¹.

HRMS *m/z* Calcd for C₁₉H₂₀Br₂O : 421.9875, found : 421.9879, **RI**: 49.0;

Calcd for C₁₉H₂₀Br⁸¹BrO : 423.9855, found : 423.9859, **RI**: 100.

Yellow oil; **R_f**: 0.64 (hexane : diethyl ether 4:1)

¹H NMR (400 MHz, CDCl₃) δ 7.30-7.16 (m, 10H), 4.12 (ddd, *J* = 4.96, 10.48, 12.12 Hz, 1H), 3.78 (t, *J* = 10.20 Hz, 1H), 3.43 (dt, *J* = 2.04, 9.52 Hz, 1H), 3.33-3.27 (m, 1H), 2.90 (ddd, *J* = 4.81, 9.80, 14.06 Hz, 1H), 2.82 (ddd, *J* = 5.36, 8.88, 13.87 Hz, 1H), 2.74-2.68 (m, 2H), 2.50-2.41 (m, 1H), 2.34 (ddd, *J* = 1.64, 4.92, 13.28 Hz, 1H), 2.00 (q, *J* = 12.24 Hz, 1H), 1.94-1.82 (m, 2H), 1.76-1.68 (m, 1H).

¹³C NMR (100 MHz, CDCl₃) δ 141.4, 141.3, 128.5, 128.4, 126.0, 125.9, 80.6, 76.1, 59.1, 53.9, 44.8, 36.8, 35.8, 31.6, 31.5.

FTIR (neat) 3024, 2947, 2920, 2859, 1495, 1454, 1155, 1124, 1084, 1051, 750, 698 cm⁻¹.

HRMS *m/z* Calcd for C₂₁H₂₄Br⁸¹BrO : 452.0168, found : 452.0179, **RI**: 100;

Calcd for C₂₁H₂₄⁸¹Br₂O : 454.0147, found : 454.0160, **RI**: 53.8.

Procedures of debromination of 2,6-crossed-4,5-dibromo-tetrahydropyran (2a).

Approach 1. To an oven-dried 25mL round-bottom flask equipped with a magnetic stirring bar was added **2a** (44.9 mg, 0.10 mmol, 1.0 equiv.) in 2.5 mL anhydrous glacial acetic acid and activated zinc (68.8 mg, 1.0 mmol, 10.0 equiv.). The reaction was allowed to proceed at room temperature for 24 hrs before diluting with diethyl ether (10 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product

was purified *via* flash chromatography (0.4% diethyl ether in hexane) to afford **4a** as pale yellow oil in 70% yield.

Approach 2. To an oven dried 25 mL round-bottom flask equipped with a magnetic stirring bar was added **2a** (24.5 mg, 0.06 mmol, 1.0 equiv.) and tributyltin hydride (0.015 mL, 0.06 mmol, 1.0 equiv.) in 1 mL anhydrous toluene and ABCCN (1,1'-azobis(cyclohexane) carbonitrile) (1.2 mg, 0.005 mmol, 0.10 equiv.). The reaction was allowed to proceed at 110 °C for 24 hrs before quenching with saturated KF solution (15 mL). The aqueous layer was extracted with diethyl ether (10 mL $\times$ 3) and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (1% diethyl ether in hexane) to afford **4a** as pale yellow oil in 71% yield.

R_f: 0.75 (hexane : diethyl ether 4:1)

¹H NMR (400 MHz, CDCl₃) δ 7.21-7.09 (m, 5H), 5.71 (ddd, J = 2.72, 5.40, 10.28 Hz, 1H), 5.60 (td, J = 1.04, 10.28 Hz, 1H), 3.76 (d, J = 1.80 Hz, 1H), 3.39-3.33 (m, 1H), 2.70 (ddd, J = 5.33, 8.95, 13.90 Hz, 1H), 2.65 (td, J = 8.28, 13.71 Hz, 1H), 1.83-1.76 (m, 4H), 1.70-1.60 (m, 5H), 1.36-1.33 (m, 1H), 1.18-1.03 (m, 5H).

¹³C NMR (100 MHz, CDCl₃) δ 142.4, 129.0, 128.6, 128.2, 125.6, 125.0, 79.0, 72.4, 42.8, 37.6, 31.6, 31.5, 28.7, 28.3, 26.6, 26.30, 26.29.

FTIR (neat) 3026, 2924, 2851, 1495, 1450, 1188, 1130, 1088, 1070, 746, 698 cm⁻¹.

HRMS m/z Calcd for C₁₉H₂₆O : 270.1978, found : 270.1967.

Procedures of elimination of 2,6-crossed-4,5-dibromo-tetrahydropyran (**2a**).

To an oven-dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added **2a** (136.3 mg, 0.32 mmol, 1.0 equiv.) in 1 mL dry ethanol and potassium *tert*-butoxide (0.64 mL, 0.64 mmol, 2.0 equiv.). The reaction was allowed to proceed at room temperature for 24 hrs before quenching with saturated ammonium chloride solution (5 mL). The aqueous layer was extracted with diethyl ether (10 mL $\times$ 3) and the combined organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (0.4% diethyl ether in hexane) to afford **4b** as colorless oil in 69% yield.

Procedures of elimination of 2,6-crossed-4,5-dibromo-tetrahydropyran (**3a**).

To an oven-dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added **3a** (86.0 mg, 0.20 mmol, 1.0 equiv.) in 2 mL dry α,α,α -trifluorotoluene and potassium *tert*-butoxide (0.40 mL, 0.40 mmol, 2.0 equiv.). The reaction was allowed to proceed at refluxing temperature ($\sim 110^\circ\text{C}$) for 24 hrs before quenching with saturated ammonium chloride solution (5 mL). The aqueous layer was extracted with diethyl ether (10 mL $\times$ 3) and the combined organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (0.4% diethyl ether in hexane) to afford **4b** as colorless oil in 59% yield

R_f: 0.79 (hexane : diethyl ether 4:1)

¹H NMR (300 MHz, CDCl₃) δ 7.23-7.09 (m, 5H), 5.96 (s, 1H), 3.77 (m, 1H), 3.47-3.38 (m, 1H), 2.70 (ddd, J = 5.49, 8.67, 13.86 Hz 1H), 2.63 (td, J = 6.01, 13.72 Hz, 1H) 2.39-2.28 (m, 1H), 2.17 (td, J = 2.92, 16.79 Hz, 1H), 1.85-1.62 (m, 8H), 1.18-0.99 (m, 5H).

¹³C NMR (75.4 MHz, CDCl₃) δ 141.8, 130.1, 128.5, 128.3, 125.8, 119.0, 80.4, 73.5, 42.6, 41.1, 36.9, 31.4, 28.7, 28.0, 26.5, 26.2, 26.1.

FTIR (neat) 2926, 2853, 1649, 1602, 1495, 1450, 1341, 1317, 1123, 746, 698 cm⁻¹.

HRMS *m/z* Calcd for C₁₉H₂₅BrO : 348.1083, found : 348.1086, **RI**: 100;

Calcd for C₁₉H₂₅⁸¹BrO : 350.1063, found : 350.1074, **RI**: 99.9.

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