Stereoselective Synthesis of *cis*- and *trans*-2,3-Disubstituted Tetrahydrofurans via Oxonium-Prins Cyclization – Access to the Cordigol Ring System

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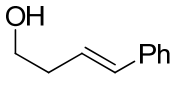
Supporting Information

General Directions

All reactions were performed under anhydrous conditions and an atmosphere of nitrogen in oven-dried glassware. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogenous materials, unless otherwise indicated. *Solvents:* were distilled unless otherwise indicated. *Reagents:* were purchased from commercial sources, handled according to COSHH regulations. *Chromatography:* Flash chromatography (FC) was performed on silica gel (Merck Kieselgel 60 F_{254} 230-400 mesh) unless otherwise indicated. Thin Layer Chromatography (TLC) was performed on Merck aluminium-backed plates pre-coated with silica (0.2 mm, 60 F_{254}) which were visualized either by quenching of ultraviolet fluorescence (λ_{max} = 254 and 366 nm) or by charring with Vanillin TLC dip. *Melting points:* were determined on a Khofler hot stage. *Infra red spectra:* were recorded as solids or neat liquids on Perkin-Elmer Paragon 1000 Fourier transform spectrometer. Only selected absorbances (υ_{max}) are reported. *^{1}H NMR spectra:* were recorded at 400 MHz on a Bruker AMX-400 instrument. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak. Coupling constants (*J*) are reported to the nearest 0.5 Hz. *^{13}C NMR spectra:* were recorded at 100 MHz on a Bruker AMX-400 instrument. Chemical shifts (δ_C) are quoted in ppm, referenced to the appropriate residual solvent peak. Degenerate peaks are suffixed by the number of carbons. *NOESY* spectra were recorded at 500 MHz on a Bruker AMX-500 instrument. *Mass spectra:* Low resolution mass spectra (*m/z*) were recorded on either a VG platform II or VG AutoSpec spectrometers, with only molecular ions (M^+, MH^+, MNH_4^+) and major peaks being reported with intensities quoted as percentages of the base peak. High Resolution Mass Spectrometry (HRMS) measurements are valid to ± 5ppm.

Experimental Procedures:

(E)-4-Phenylbut-3-en-1-ol[1]



Chemical Formula: $C_{10}H_{12}O$
Exact Mass: 148.09
Molecular Weight: 148.20

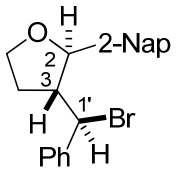
[1] Charette, A. B.; Juteau, H.; Lebel , H; Molinaro, C. *J. Am. Chem. Soc.*, **1998**, *120*, 11943.

To a round bottomed flask containing *trans*-3-styryl acetic acid (2 g, 12.4 mmol), and THF (10 mL), was added Lithium aluminium hydride (15 mL, 15 mmol, 1 M solution in THF) dropwise. The reaction was stirred at 0 °C for 20 min, and at RT for 40 min. It was then quenched with H_2O (0.7 mL), followed by 10% NaOH solution (2 mL). The reaction mixture was then filtered through Celite®, and the solvent removed under reduced pressure. The resulting red oil was purified by FC eluting with EtOAc:Hexane (15:85) to yield *(E)*-4-phenylbut-3-en-1-ol as a clear colourless oil (1.6 g, 87% yield). υ_{max} (CH_2Cl_2): 3340 (O-H), 3029, 2935, 2880, 1738 (C=C), 1598, 1495, 1448, 1243, 1045 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400MHz): 2.5 (2H, dt, CH_2CH_2, *J* = 7.2, 6 Hz), 3.78 (2H, t, OCH_2CH_2, *J* = 6 Hz), 6.23 (1H, dt, C=C*H*, *J* = 15.6, 7.2 Hz), 6.52 (1H, d, C=C*H, J* = 15.6 Hz) 7.32 (5H, m, CH_{Ar}), OH absent; **^{13}C NMR** ($CDCl_3$, 100MHz): 36.3 (t), 62.0 (t), 126.1 (2 × d), 126.4 (d), 127.3 (d), 128.6 (2 × d), 132.8 (d), 137.2 (s); *m/z* (ESI): 149 (MH^+, 20%), 130 (85), 117 (100), 91 (50); Found: *m/z* (CI) MNH_4^+ 166.1228 $C_{10}H_{16}NO$ requires 166.1232 (Δ=-2.3 ppm).

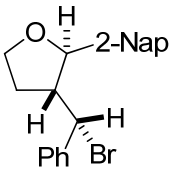
General Procedure for Oxonuim-Prins Reactions:

To a 50 mL round-bottomed-flask containing *(E)*-4-phenylbut-3-en-1-ol (0.57 mmol) and aldehyde (0.57 mmol) in CH_2Cl_2 (4 mL) at -78 °C was added solid tin(IV) bromide (0.28 g, 0.6 mmol) and TMS-Br (79 μL, 0.6 mmol). The reaction was stirred at -78 °C until the homoallylic alcohol **1** was seen to be consumed by TLC before being quenched with saturated $NaHCO_3$ solution (4 mL). The reaction was allowed to warm to RT before adding further $NaHCO_3$ (4 mL). The organic layer was then separated, the aqueous layer extracted further with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts washed with brine (3 × 10 mL), and dried over $MgSO_4$. Following this it was filtered and the solvent was removed under reduced pressure. The reaction mixture was then purified by FC eluting with EtOAc:Petrol ether or diethyl ether:pentane mixtures to yield the substituted THF.

3-[Bromo(phenyl)methyl]-2-(naphthalen-2-yl)tetrahydrofuran 1 (Table 1, entry 4)



1a
(2,3-*trans*)



1b
(2,3-*trans*)

Chemical Formula: $C_{21}H_{19}BrO$
Exact Mass: 366.06
Molecular Weight: 367.28

Using the general procedure, *(E)*-4-phenylbut-3-en-1-ol (100 mg, 0.67 mmol) and 2-naphthaldehyde (100 mg, 0.67 mmol) after 4 h, purifying by FC eluting with EtOAc:Petrol Ether (1:20) yielded the THF **1** as a thick clear colourless oil (120 mg, 48% yield) comprising an inseparable mixture of three diastereoisomers (**1a**:**1b**, 90:10 by ^{1}H NMR integration). υ_{max} (CH_2Cl_2, cm^{-1}): 3057, 2935, 2865, 1735, 1715, 1601, 1512, 1496, 1455, 1243, 1063; *m/z* (CI): 304 [$(M-H^{79}Br)NH_4^+$, 90%] 287 (100), 190 (20), 174 (20); Found: *m/z* (CI) $(M-H^{79}Br)NH_4^+$, 304.1705 $C_{21}H_{22}NO$ requires 304.1701 (Δ=1.2 ppm).

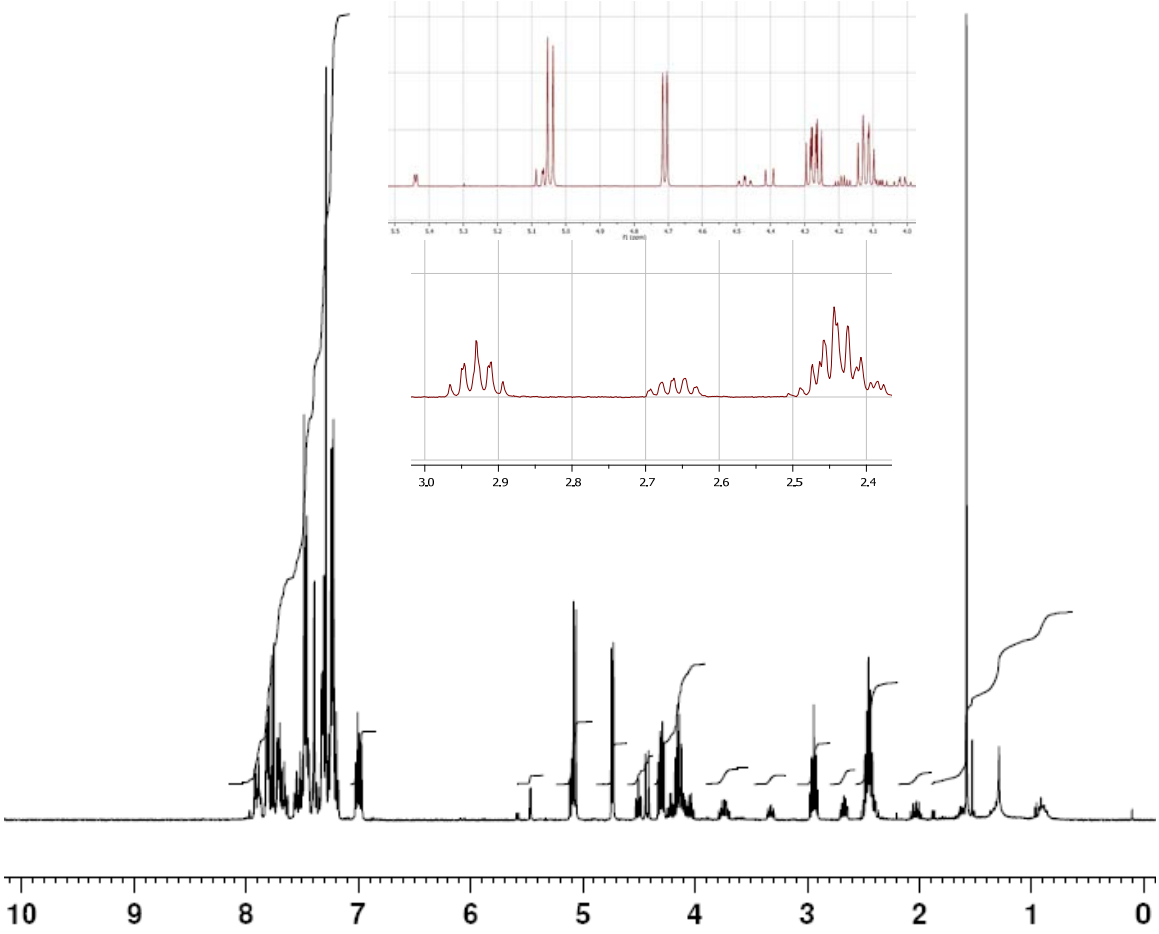
(2*R**,3*R**,1'*R**)-*THF* **1a**: **^{1}H NMR** ($CDCl_3$, 400MHz): 2.45 (2H, m, OCH_2CH_2), 2.93 (1H, dddd, OCH(Nap)C*H*, *J* = 8, 6.4, 6, 1.6 Hz), 4.13 (1H, m, OCH_2), 4.29 (1H, ddd, OCH_2, *J* = 7.2, 6, 1.2 Hz), 4.72 (1H, d, *J* = 6 Hz), 5.06 (1H, d, *J* = 8 Hz), 6.96-7.01 (2H, m, CH_{Ar}), 7.18-7.31 (5H, m, CH_{Ar}), 7.45-7.47 (2H, m, CH_{Ar}), 7.70 (1H, m, CH_{Ar}), 7.53 (1H, d, *J* = 8.4Hz, CH_{Ar}), 7.81 (1H, m, CH_{Ar}); **^{13}C NMR** ($CDCl_3$, 100MHz): 31.7 (t), 56.9 (t), 57.5 (d), 67.9 (d), 84.1 (d), 123.7 (s), 125.2 (d), 125.8 (2 × d), 126.0 (d), 126.1 (d), 127.6 (d), 127.8 (d), 127.9 (2 × d),128.2 (d), 128.5 (d), 132.9 (s), 133.0 (s), 138.9 (s), 140.7 (s)

(2*R**,3*R**,1'*S**)-*THF* **1b**: **^{1}H NMR** ($CDCl_3$, 400MHz) - distinguishable/diagnostic peaks only: 2.45 (1H, m, OCH_2CH_2), 2.66 (1H, m, OCH_2CH_2), 3.73 (1H, m, OCH(Nap)C*H*), 4.13 (1H, m, OCH_2), 4.40 (1H, d, OC*H*(Ph)Br, *J* = 11.6 Hz), 4.49 (1H, t, OCH_2, *J* = 8.4 Hz), 5.10 (1H, m, OC*H*(Nap)), 5.45 (1H), d, C*H*Ph, *J* = 5 Hz).

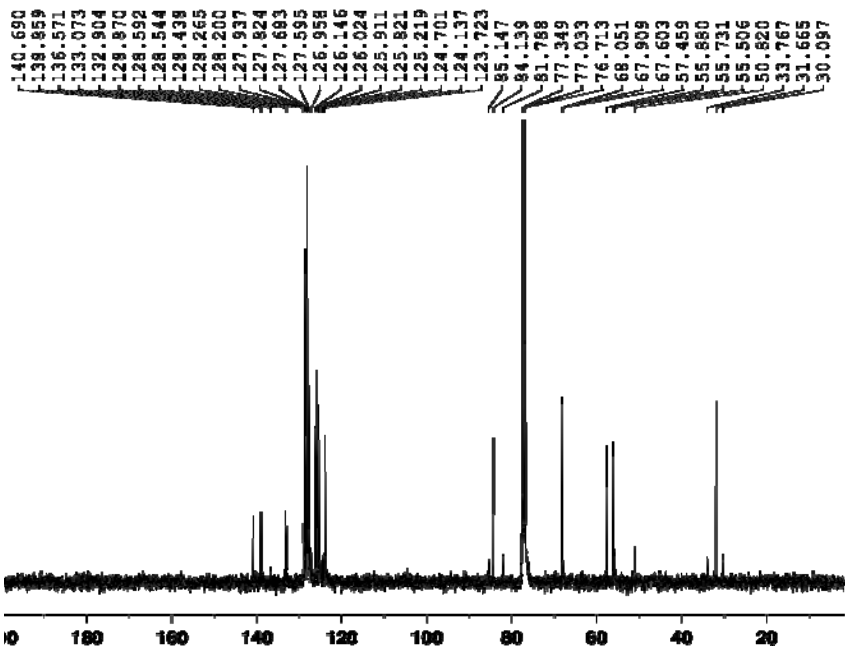
NOE Table

1a		**1b**	
	4.72 ppm (H-2)		5.1 ppm (H-2)
5.06 ppm (H-1')	✓	5.45 ppm (H-1')	✓

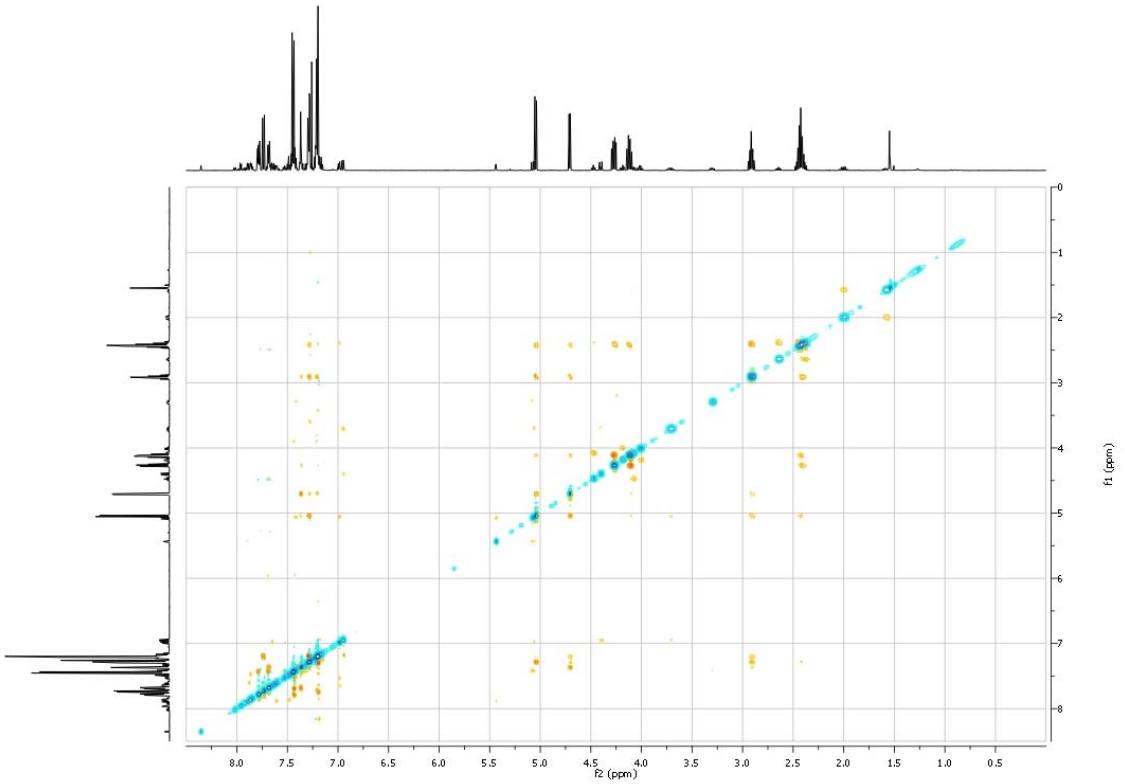
^{1}H NMR (1a:1b, 90:10)



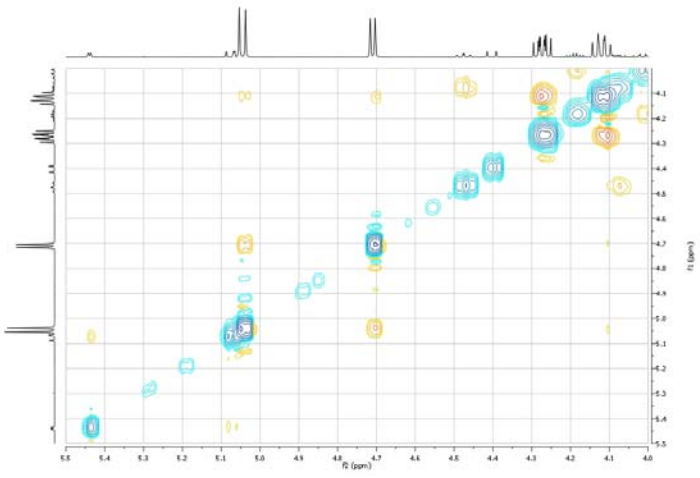
^{13}C NMR (1a:1b, 90:10)



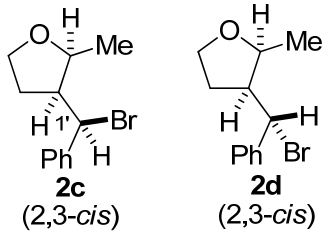
NOESY (1a:1b, 90:10)



NOESY Expansion (1a:1b, 90:10)



3-[Bromo(phenyl)methyl]-2-methyltetrahydrofuran 2 (Table 2, entry 1)



Chemical Formula: $C_{12}H_{15}BrO$
Exact Mass: 254.03
Molecular Weight: 255.15

Using the general procedure, *(E)*-4-phenylbut-3-en-1-ol (80 mg, 0.54 mmol) and acetaldehyde (70 mg, 0.54 mmol) after 1.5 h, purifying by FC eluting with diethyl ether:pentane (1:1), yielded the THF **2** as a thick clear colourless oil (60 mg, 55% yield) comprising an inseparable mixture of two diastereoisomers (**2c**:**2d**, 60:40 by ^{1}H NMR integration). υ_{max} (CH_2Cl_2): 2973, 2931, 2875, 1497, 1456, 1415, 1378, 1151 cm^{-1}; *m/z* (CI): 272/274 (MNH_4^+, 100%), 236 (60), 192 (70), 175 (20), 132 (90); Found: *m/z* (CI) MNH_4^+ 272.0650, $C_{12}H_{19}NO^{79}Br$ requires 272.0650 (Δ=0.0 ppm).

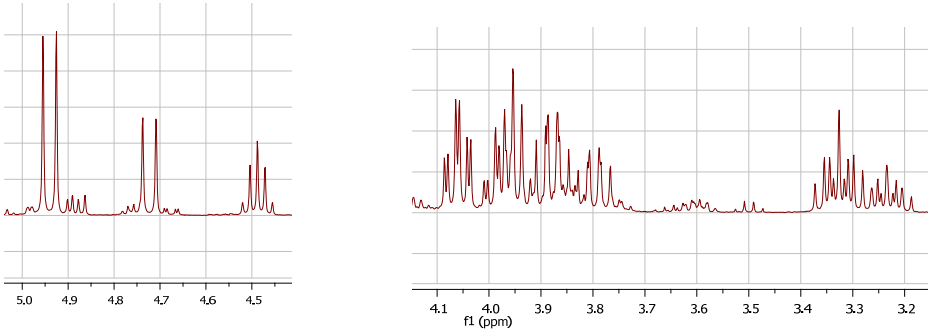
(2*S**,3*S**,1'*R**)-*THF* **2c**: **^{1}H NMR** ($CDCl_3$, 400MHz): 0.88 (3H, d, C*H*$_3$, *J* = 6.5 Hz), 2.09 (1H, ddt, OCH_2CH_2), 2.50 (1H, dtd, OCH_2CH_2), 3.34 (1H, ddd, OCH(Me)C*H*, *J* = 12, 9.2, 7.2 Hz), 3.89 (1H, ddd, OC*H*$_2$, *J* = 9.3, 8.6, 7.2 Hz), 3.96 (1H, dq, OC*H*Me, *J* = 7, 6.4 Hz), 4.07 (1H, td, OC*H*$_2$, *J* = 8.8, 2.7), 4.95 (1H, d, C*H*Ph, *J* = 11.5 Hz), 7.29-7.47 (5H, m, C*H*$_{Ar}$); **^{13}C NMR** ($CDCl_3$, 100MHz): 15.7 (t), 32.4 (t), 49.8 (d), 55.4 (d), 65.8 (d), 74.9 (d), 128.4 (2 × d), 128.7 (d), 128.9 (2 × d), 141.2 (s).

(2*S**,3*S**,1'*S**)-*THF* **2d**: **^{1}H NMR** ($CDCl_3$, 400MHz) – distinguishable/diagnostic peaks only: 1.30 (3H, d, C*H*$_3$, *J* = 6.4 Hz), 1.40-1.62 (2H, m, OCH_2CH_2), 3.24 (1H, m, OCH(Me)C*H*), 3.81 (1H, m, OC*H*$_2$), 4.50 (1H, dq, OC*H*Me, *J* = 7, 6.4 Hz), 4.74 (1H, d, CHBrPh, *J* = 12 Hz), 7.31-7.46 (5H, m, C*H*$_{Ar}$).

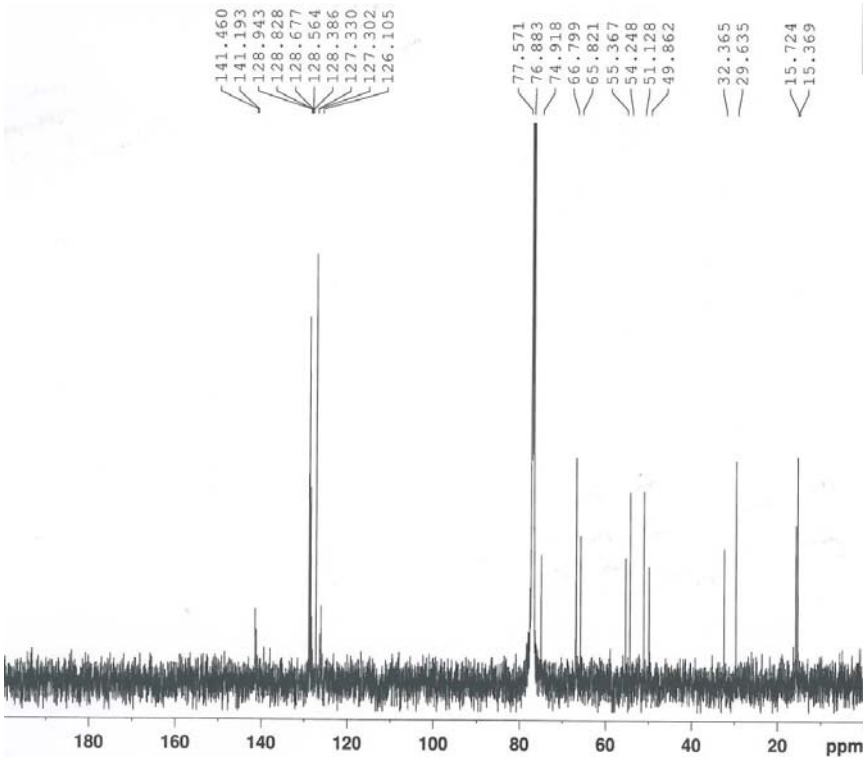
NOE Table

2c		**2d**	
	3.96 ppm (H-2)		4.5 ppm (H-2)
4.95 ppm (H-1')	×	4.74 ppm (H-1')	×

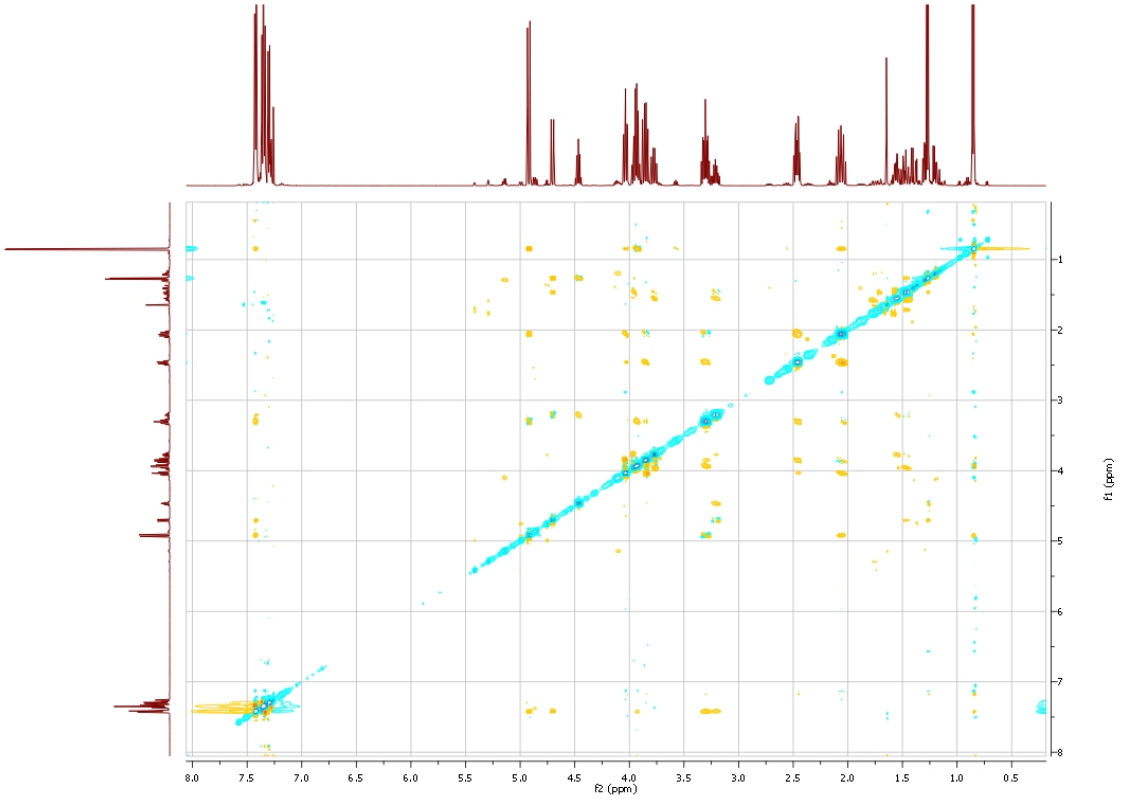
^{1}H NMR (2c:2d, 60:40)



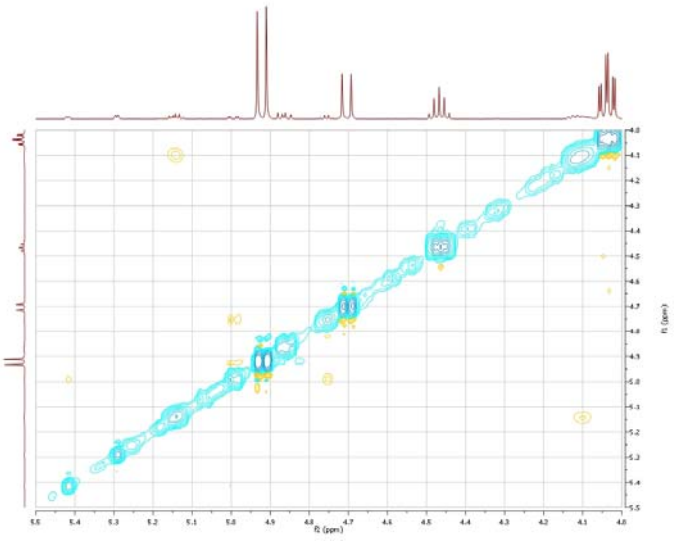
^{13}C NMR (2c:2d, 60:40)



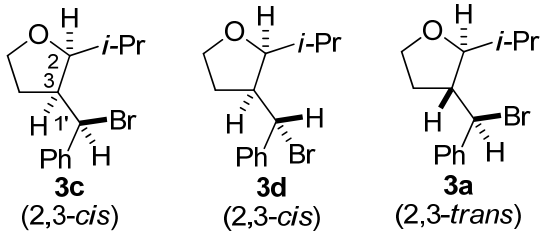
NOESY (2c:2d, 60:40)



NOESY Expansion (2c:2d, 60:40)



3-[Bromo(phenyl)methyl]-2-isopropyltetrahydrofuran 3 (Table 2, entry 2)



Chemical Formula: $C_{14}H_{19}BrO$
Exact Mass: 282.06
Molecular Weight: 283.20

Using the general procedure, *(E)*-4-phenylbut-3-en-1-ol (100 mg, 0.68 mmol) and isobuteraldehyde (70 mg, 0.68 mmol) after 3 h, purifying by FC eluting with EtOAc:Pet Ether (1:20), yielded the THF **3** as a white solid (175 mg, 92% yield) comprising an inseparable mixture of three diastereoisomers (**3c**:**3d**:**3a**, 80:12:8 by ^{1}H NMR integration). m.p. 70-71 °C; υ_{max} (CH_2Cl_2): 2957, 2928, 2871, 1499, 1467, 1454, 1388, 1370, 1205, 1178, 1046 cm^{-1}; *m/z* (CI): 300/302 (MNH_4^+, 100%), 220 (80), 203 (50); Found: *m/z* (CI) (M-H^{79}Br)NH_4^+ 220.1707, $C_{14}H_{22}NO$ requires 220.1701 (Δ=2.5 ppm).

(2*S**,3*S**,1'*R**)-*THF* **3c**: **^{1}H NMR** ($CDCl_3$, 400MHz): 0.74 (3H, d, CHC*H*$_3$, *J* = 6.8 Hz), 1.01 (3H, d, CHC*H*$_3$, *J* = 6.8 Hz), 1.64 (1H, m, C*H*(Me)$_2$), 2.27 (1H, m, OCH$_2$C*H*$_2$), 2.38 (1H, m, OCH$_2$C*H*$_2$), 3.22 (1H, m, OCH(^{i}Pr)C*H*), 3.62 (1H, dd, OC*H*(^{i}Pr), *J* = 5.2, 7.0 Hz), 3.87 (1H, m, OC*H*$_2$), 4.12 (1H, m, OC*H*$_2$), 5.24 (1H, d, C*H*Ph, *J* = 9.2 Hz), 7.30-7.48 (5H, m, C*H*$_{Ar}$); **^{13}C NMR** ($CDCl_3$, 100MHz): 18.8 (q), 21.1 (q), 28.7 (d), 32.8 (t), 48.6 (t), 55.0 (d), 66.9 (d), 84.9 (d), 127.4 (2 × d), 128.5 (d), 128.9 (2 × d), 141.9 (s).

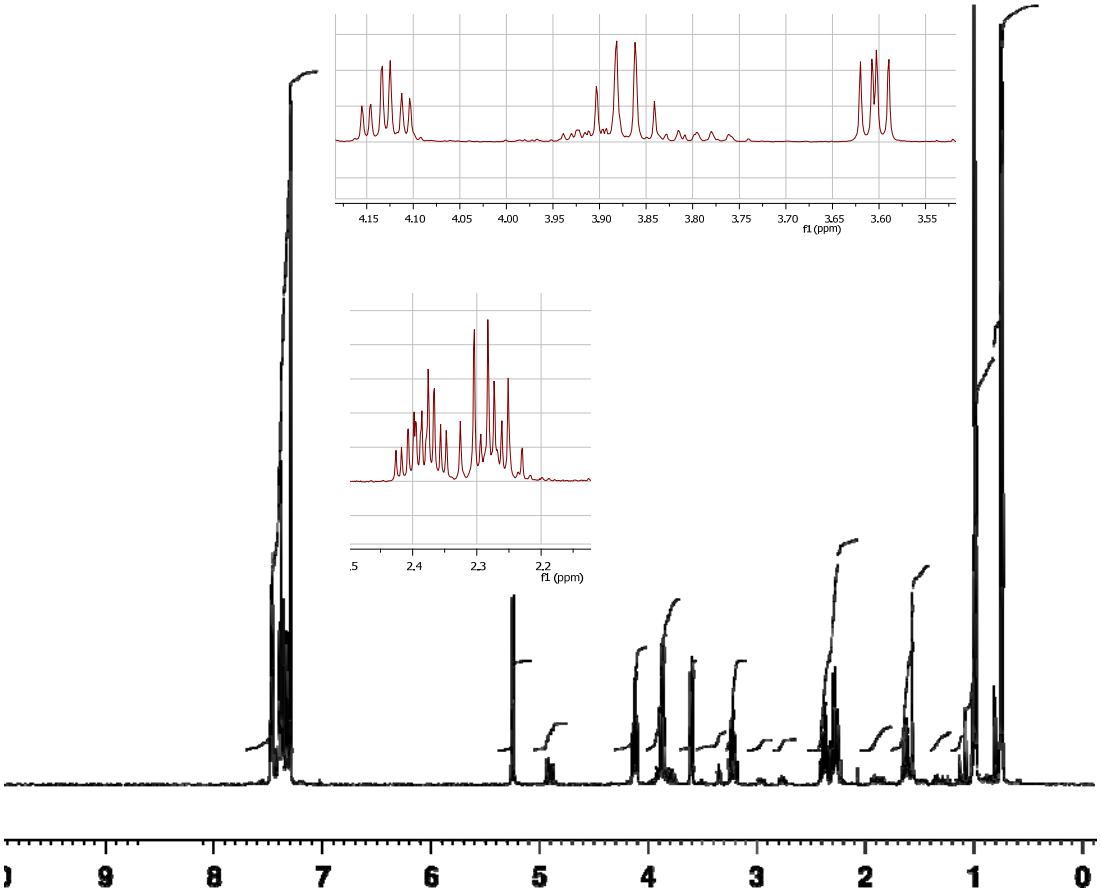
(2*S**,3*S**,1'*S**)-*THF* **3d**: **^{1}H NMR** ($CDCl_3$, 400MHz) - distinguishable/diagnostic peaks only: 0.81 (3H, d, CHC*H*$_3$, *J* = 6.8 Hz), 1.10 (3H, d, CHC*H*$_3$, *J* = 6.8 Hz), 1.17 (1H, m, C*H*(Me)$_2$), 2.22-2.43 (2H, m, OCH$_2$C*H*$_2$), 2.77 (1H, dddd, OCH(^{i}Pr)C*H*, *J* = 8.4, 5.2, 4.8, 4 Hz), 3.35 (1H, dd, OC*H*(^{i}Pr), *J* = 5.2, 5.2 Hz), 3.74-3.94 (2H, m, OC*H*$_2$), 4.90 (1H, d, C*H*Ph, *J* = 8.8 Hz), 7.30-7.50 (5H, m, C*H*$_{Ar}$).

(2*S**,3*R**,1'*R**)-*THF* **3a**: **^{1}H NMR** ($CDCl_3$, 400MHz) distinguishable/diagnostic peaks only: 1.01 (3H, d, CHC*H*$_3$, *J* = 6.4 Hz), 1.08 (3H, d, CHC*H*$_3$, *J* = 6.8 Hz), 1.48 (1H, m, OCH$_2$C*H*$_2$), 1.86 (1H, m, OCH$_2$C*H*$_2$), 1.92 (1H, m, C*H*(Me)$_2$), 2.97 (1H, dddd, C*H*C(H)(OH)(Ph), *J* = 13, 6.8, 3.6, 1.2 Hz), 3.75-3.85 (2H, m, OC*H*$_2$CH$_2$), 3.93 (1H, dd, OC*H*(^{i}Pr), *J* = 6, 3.6 Hz), 4.88 (1H, d, C*H*(OH)(Ph), *J* = 6.8 Hz), 7.30-7.50 (5H, m, C*H*$_{Ar}$).

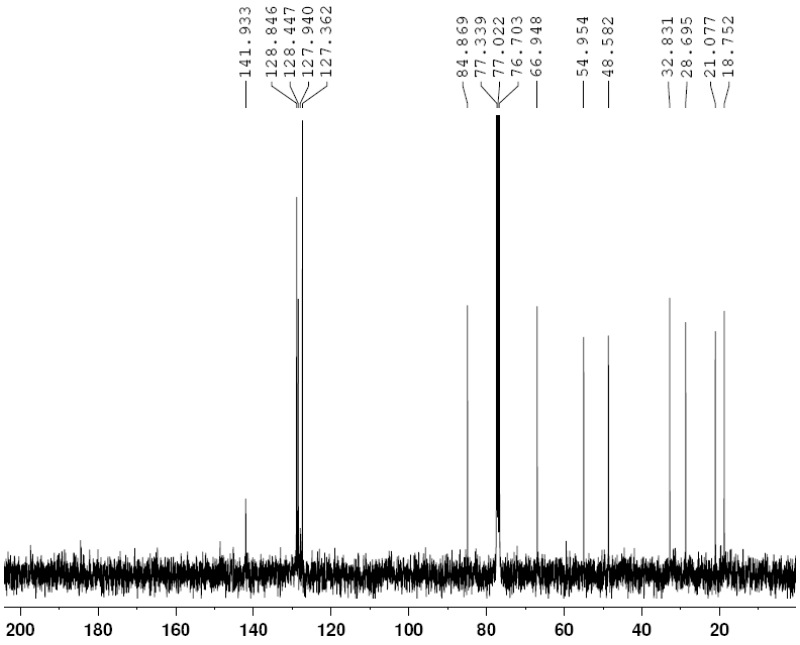
NOE Table

3c		**3d**		**3a**	
	3.62 ppm (H-2)		2.77 ppm (H-2)		4.5 ppm (H-2)
5.24 ppm (H-1')	×	4.90 ppm (H-1')	×	4.74 ppm (H-1')	✓

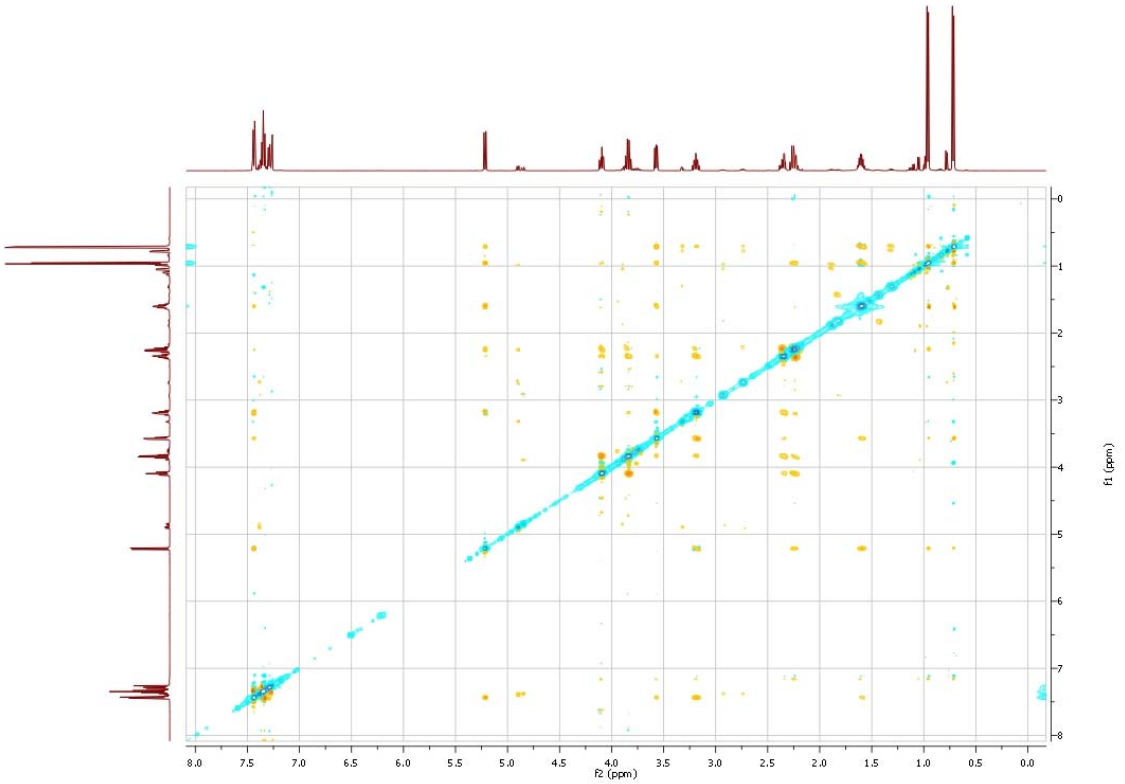
^{1}H NMR (3c:3d:3a, 80:12:8)



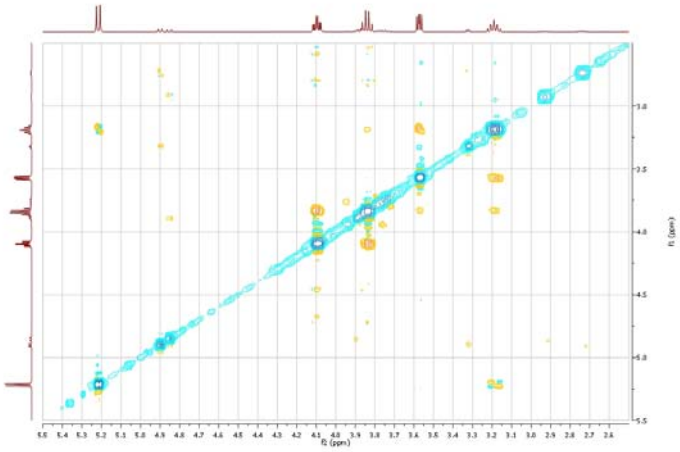
^{13}C NMR (3c:3d:3a, 80:12:8)



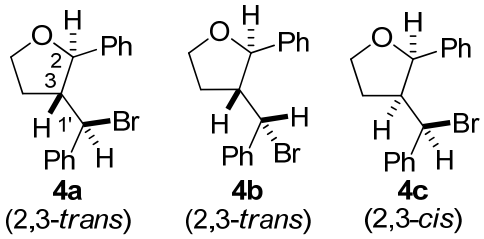
NOESY (3c:3d:3a, 80:12:8)



NOESY Expansion (3c:3d:3a, 80:12:8)



3-[Bromo(phenyl)methyl]-2-phenyltetrahydrofuran 4 (Table 2, entry 3)



Chemical Formula: $C_{17}H_{17}BrO$
Exact Mass: 316.05
Molecular Weight: 317.22

Using the general procedure, *(E)*-4-phenylbut-3-en-1-ol (100 mg, 0.67 mmol) and benzaldehyde (70 mg, 0.67 mmol) after 1.5 h, purifying by FC eluting with diethyl ether:pentane (1:1), yielded the THF **4** as a clear colourless solid (125 mg, 60% yield) comprising an inseparable mixture of three diastereoisomers (**4a**:**4b**:**4c**, 77:12:11 by ^{1}H NMR integration). υ_{max} (CH_2Cl_2): 3062, 3033, 2927, 2869, 1605, 1587, 1495, 1454, 1212, 1161 cm^{-1}; *m/z* (CI): 334/336 (MNH_4^+, 100%), 256 (15), 237 (50), 167 (20), 96 (100); Found: *m/z* (CI) MNH_4^+ 334.0811 $C_{17}H_{21}NO^{79}Br$ requires 334.0807 (Δ=1.3 ppm).

(2*R**,3*R**,1'*R**)-*THF* **4a**: **^{1}H NMR** ($CDCl_3$, 400MHz): 2.35-2.45 (2H, m, OCH_2CH_2), 2.90 (1H, dddd, OCH(Ph)C*H*, *J* = 8, 6.4, 6, 1.6 Hz), 4.09 (1H, m, OCH_2CH_2), 4.22 (1H, m, OCH_2CH_2), 4.57 (1H, d, OC*H*Ph, *J* = 6.4 Hz), 5.03 (1H, d, CH(Br)Ph, *J* = 8 Hz), 7.07 (2H, m, CH_{Ar}) 7.23-7.34 (7H, m, CH_{Ar}); **^{13}C NMR** ($CDCl_3$, 100MHz): 31.6 (d), 55.9 (d), 57.5 (s), 67.9 (s), 126.0 (d), 127.5 (d), 127.7 (2 × d), 127.8 (d), 127.8 (2 × d), 127.9 (d), 128.3 (2 × d), 128.4 (d), 128.5 (s), 128.6 (s).

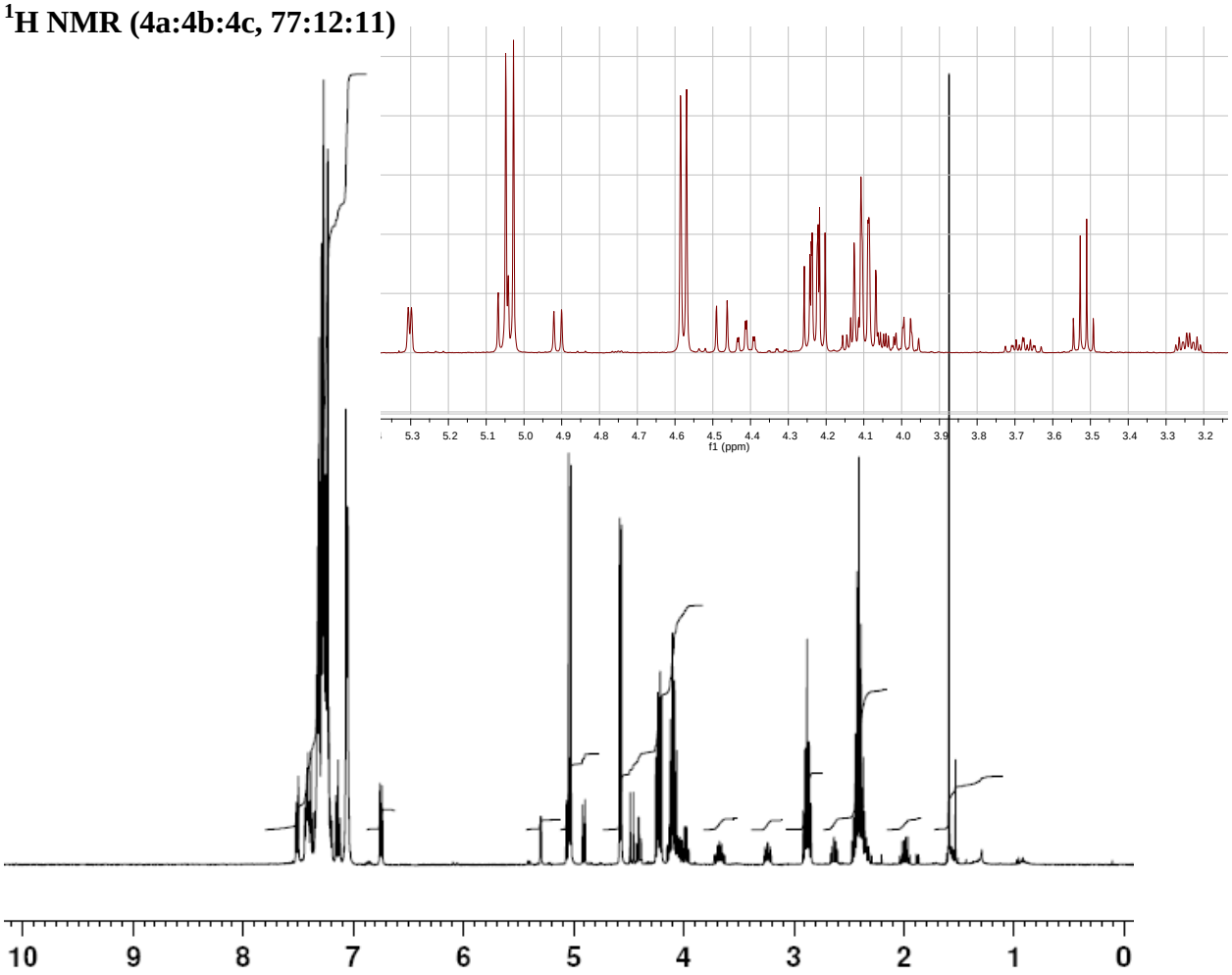
(2*R**,3*R**,1'*S**)-*THF* **4b**: **^{1}H NMR** ($CDCl_3$, 400MHz) - distinguishable/diagnostic peaks only: 1.58 (1H, m, OCH_2CH_2), 2.0 (1H, m, OCH_2CH_2), 3.23 (1H, m, OCH(Ph)C*H*), 4.01-4.12 (2H, m, OCH_2), 4.45 (1H, d, C*H*BrPh, *J* = 11.6 Hz), 4.90 (1H, d, OC*H*Ph, *J* = 5.8 Hz).

(2*R**,3*S**,1'*R**)-*THF* **4c**: **^{1}H NMR** ($CDCl_3$, 400MHz) - distinguishable/diagnostic peaks only: 2.38 (1H, m, OCH_2CH_2), 2.61 (1H, m, OCH_2CH_2), 3.68 (1H, m, OCH(Ph)C*H*), 4.15 (1H, m, OCH_2), 4.40 (1H, m, OCH_2), 5.02 (1H, d, C*H*BrPh, *J* = 10.8 Hz), 5.33 (1H, d, OC*H*Ph, *J* = 3.2 Hz), 6.75 (2H, m, C*H*Ar).

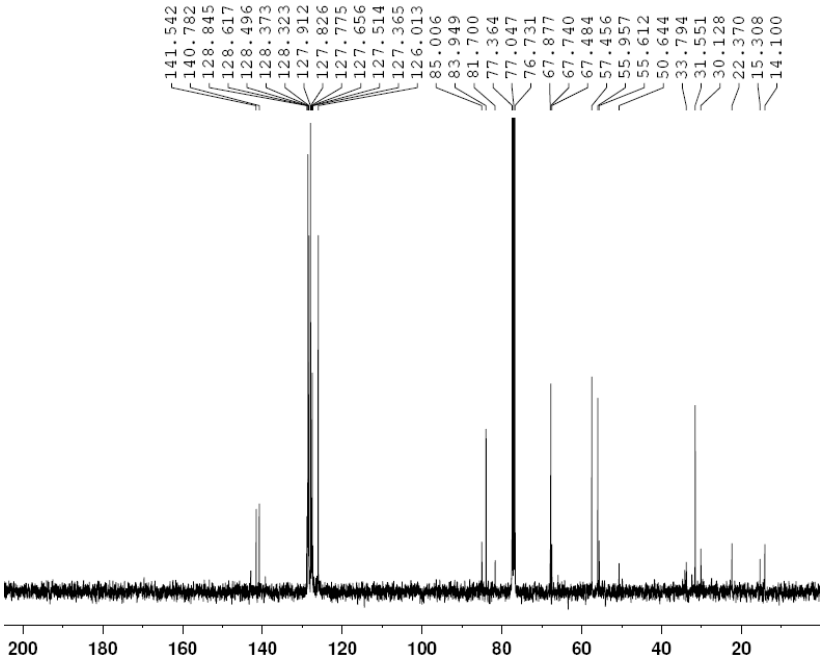
NOE Table

4a		**4b**		**4c**	
	4.57 ppm (H-2)		4.90 ppm (H-2)		5.33 ppm (H-2)
5.03 ppm (H-1')	✓	4.45 ppm (H-1')	✓	5.02 ppm (H-1')	✖

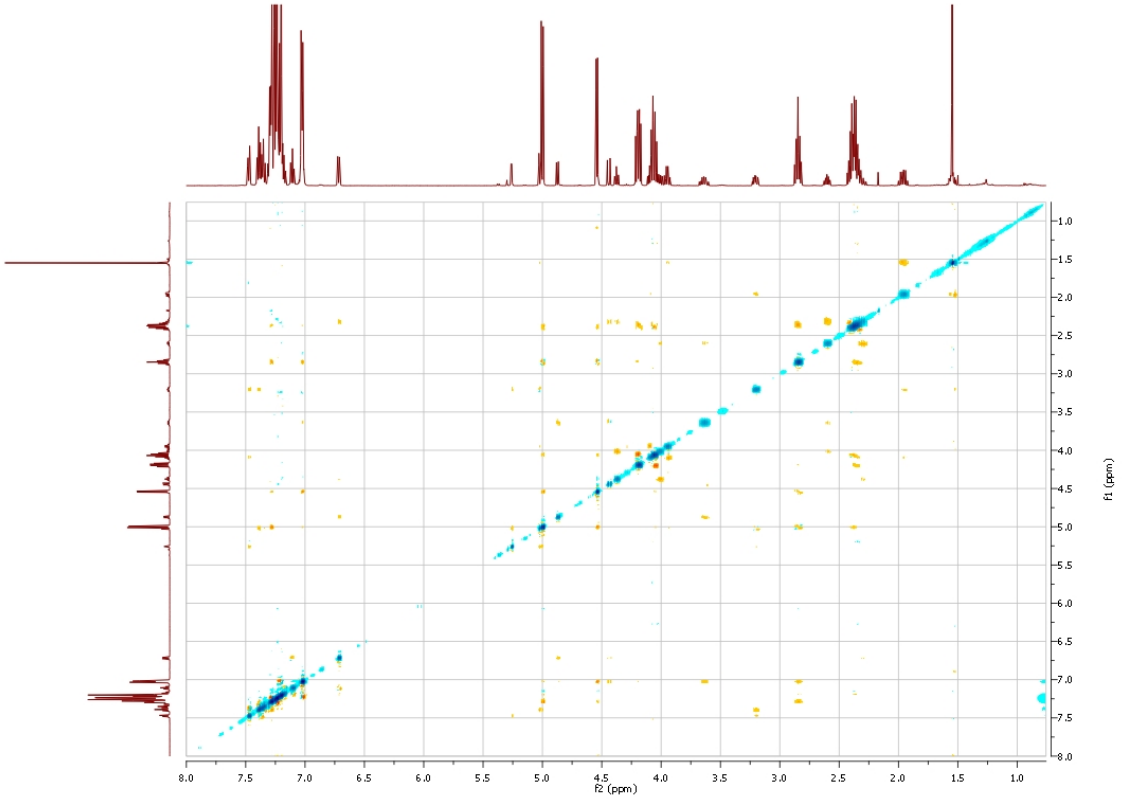
^{1}H NMR (4a:4b:4c, 77:12:11)



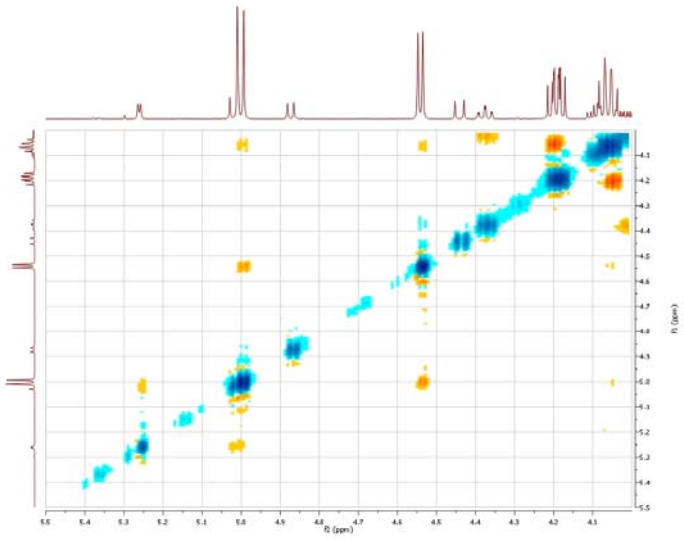
^{13}C NMR (4a:4b:4c, 77:12:11)



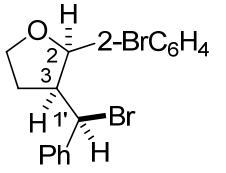
NOESY (4a:4b:4c, 77:12:11)



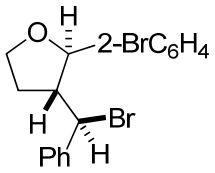
NOESY Expansion (4a:4b:4c, 77:12:11)



3-[Bromo(phenyl)methyl]-2-(2-bromophenyl)tetrahydrofuran 5 (Table 2, entry 4)



5c
(2,3-*cis*)



5a
(2,3-*trans*)

Chemical Formula: $C_{17}H_{16}Br_2O$
Exact Mass: 393.96
Molecular Weight: 396.12

Using the general procedure, *(E)*-4-phenylbut-3-en-1-ol (60 mg, 0.4 mmol) and 2-bromobenzaldehyde (0.04 mL, 0.4 mmol) after 2 h, yielded a pale yellow oil comprising THF **5** as a mixture of two diastereoisomers (**5a**:**5b**, 72:28 by ^{1}H NMR integration). The isomers were separated by FC eluting with diethyl ether:pentane (1:1) to give:

(2*R**,3*S**,1'*R**)-*THF* **5c** as a yellow oil (40mg, 27% yield): υ_{max} (CH_2Cl_2): 3064, 2931, 2881, 1573 1497, 1463, 1453, 1436, 1247, 1206, 1165, 1118, 1060 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400MHz): 2.49-2.65 (2H, m, OCH_2CH_2), 3.60-3.67 (1H, m, OCH(Ph-Br)C*H*), 3.92 (1H, m, OCH_2), 4.36 (1H, td, OCH_2, *J* = 8.2, 4.4 Hz), 4.74 (1H, d, C*H*(Br)(Ph), *J* = 8.4 Hz), 5.17 (1H, d, OC*H*(Ph-Br), *J* = 7.15 Hz), 7.03-7.07 (3H, m, CH_{Ar}), 7.12-7.16 (3H, m, CH_{Ar}), 7.22 (1H, dd, C(Br)CH_{Ar}, *J* = 8.0, 1.2), 7.32 (1H, dt, CH_{Ar}, *J* = 7.5, 1.1 Hz), 7.65 (1H, dd, OCHCCH_{Ar}, *J* = 7.8, 1,7); **^{13}C NMR** ($CDCl_3$, 100MHz): 33.3 (t), 48.0 (t), 57.5 (d), 66.9 (d), 81.7 (d), 123.1 (s), 127.1 (d), 127.4 (d), 127.8 (2 × d), 128.3 (d), 129.0 (2 × d), 129.4 (d), 132.3 (d), 137.5 (s), 141.2 (s); *m/z* (CI): 412/414/416/418 (MNH_4^+, 100%), 334 (50), 317 (60); Found: *m/z* (CI) MNH_4^+ 411.9907 $C_{17}H_{20}NO^{79}Br_2$ requires 411.9912 (Δ=-1.1 ppm).

NOE Table

5c	
	5.17 ppm (H-2)
4.74 ppm (H-1')	×

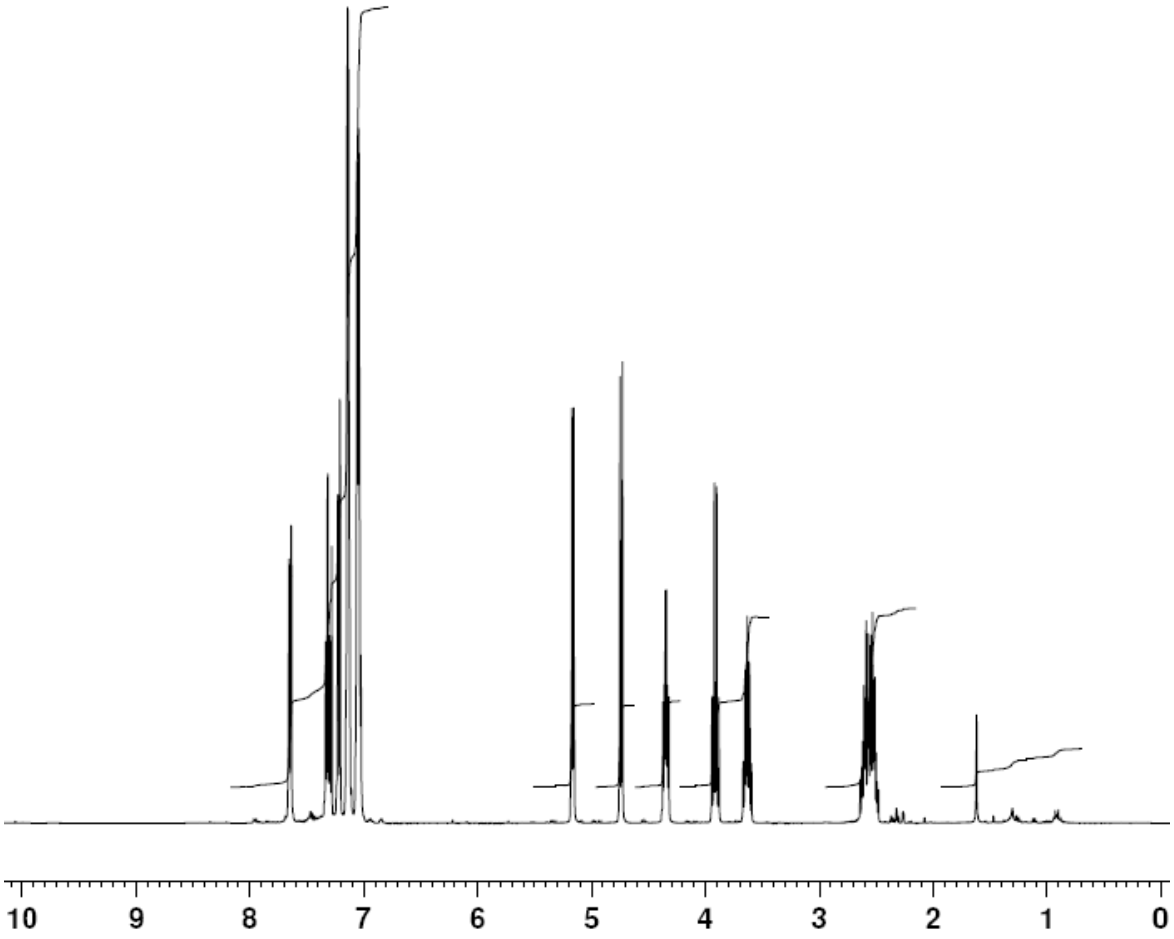
(2*R**,3*R**,1'*R**)-*THF* **5a** as a pale yellow oil (70 mg, 44% yield): υ_{max} (CH_2Cl_2): 3064, 2931, 2881, 1573, 1497, 1463, 1453, 1436, 1247, 1206, 1165, 1118, 1060 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400MHz): 2.45 (2H, m, OCH_2CH_2), 3.01 (1H, m, OCH(Ph)C*H*), 4.15 (1H, ddd, OCH_2, *J* = 8, 7.8, 7.6 Hz), 4.27 (1H, ddd, OCH_2 *J* = 7.8, 7.6, 6 Hz), 5.03 (1H, d, OC*H*(Ph-Br), *J* = 6.8 Hz), 5.20 (1H, d, OC*H*(Ph), *J* = 7.6 Hz), 7.08 (1H, dd,

C(Br)C(H)CH_{Ar} J = 7.2, 2 Hz), 7.20 (3H, m, CH_{Ar}), 7.27 (1H, m, CH_{Ar}), 7.31 (3H, m, CH_{Ar}), 7.41 (1H, dd, CH_{Ar}C(Br), J = 8, 1.2 Hz); **^{13}C NMR** ($CDCl_3$, 100MHz): 31.8 (t), 54.8 (t), 57.4 (d), 68.1 (d), 83.0 (d), 122.8 (s), 127.5 (d), 127.7 (d), 128.0 (d), 128.3 (2 × d), 128.7 (2 × d), 129.1 (d), 132.9 (d), 140.3 (s), 140.5 (s); *m/z* (CI): 412/414/416/418 (MNH_4^+, 100%), 334 (50), 317 (60); Found: *m/z* (CI) MNH_4^+ 411.9911 $C_{17}H_{20}NO^{79}Br_2$ requires 411.9912 (Δ=-0.1 ppm).

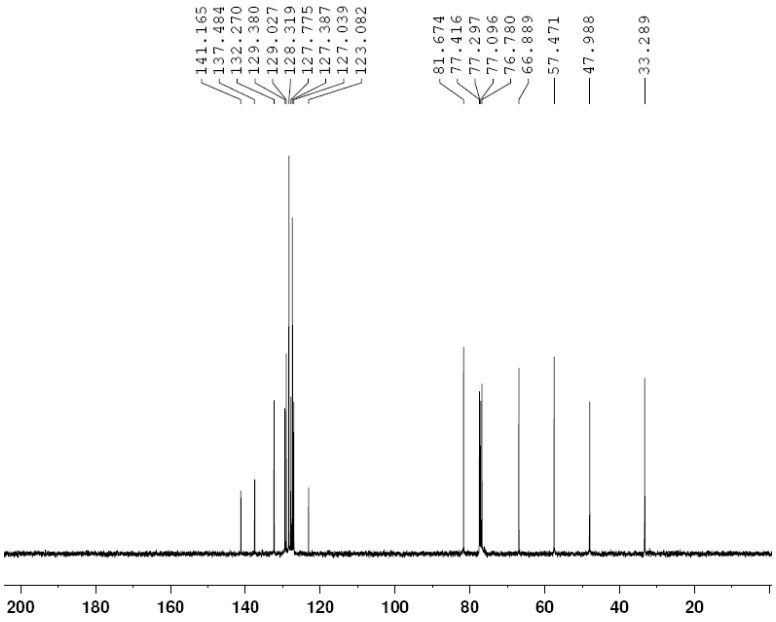
NOE Table

5a	
	5.20 ppm (H-2)
5.03 ppm (H-1')	✓

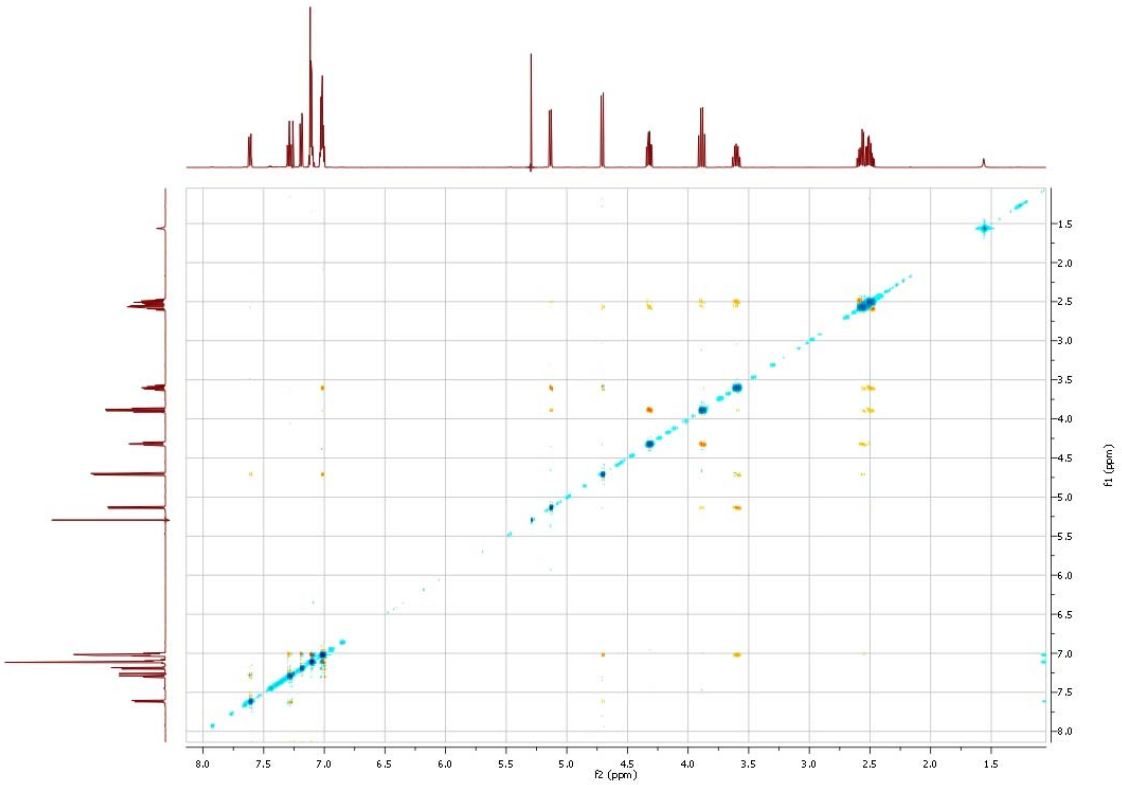
^{1}H NMR 5c



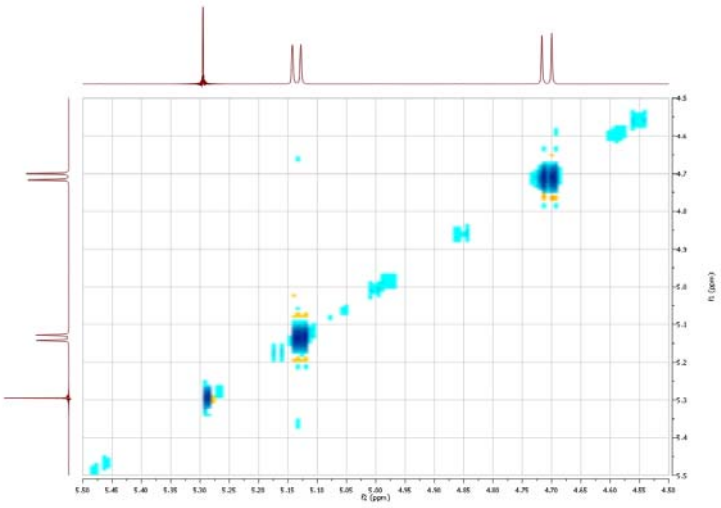
^{13}C NMR 5c



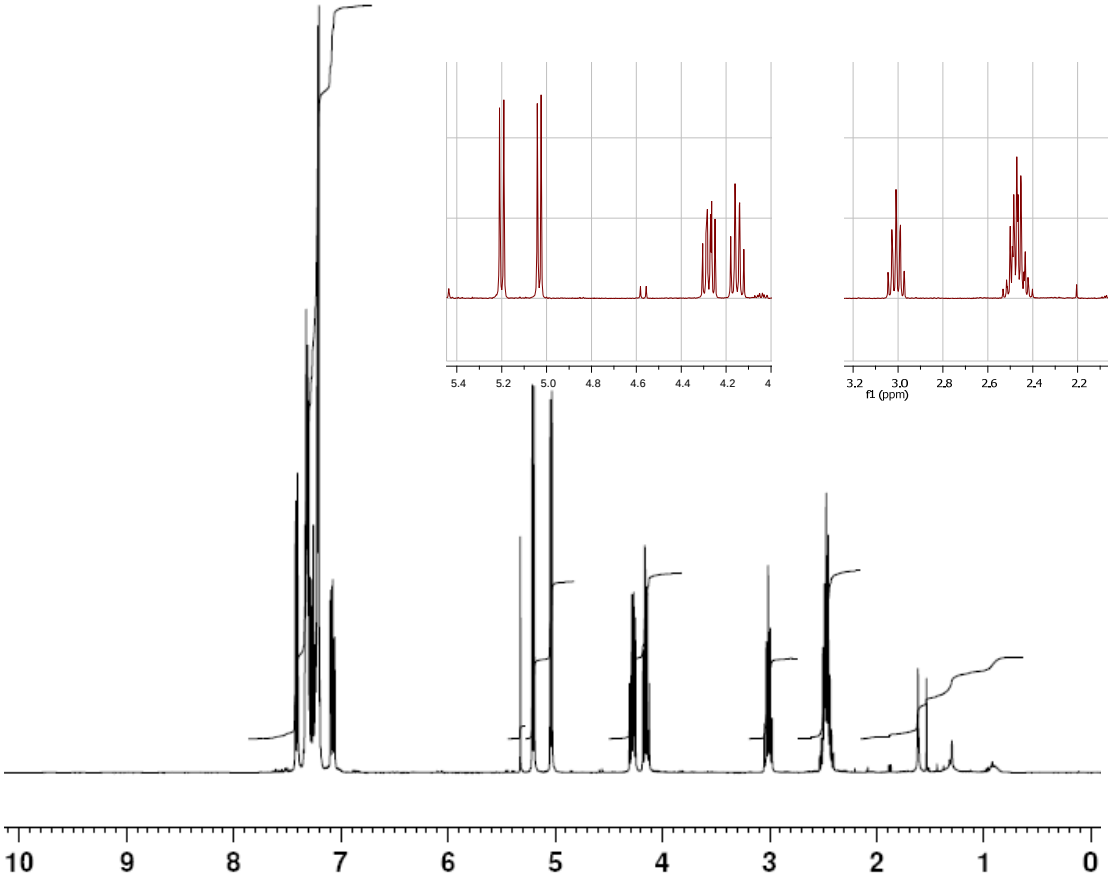
NOESY5c



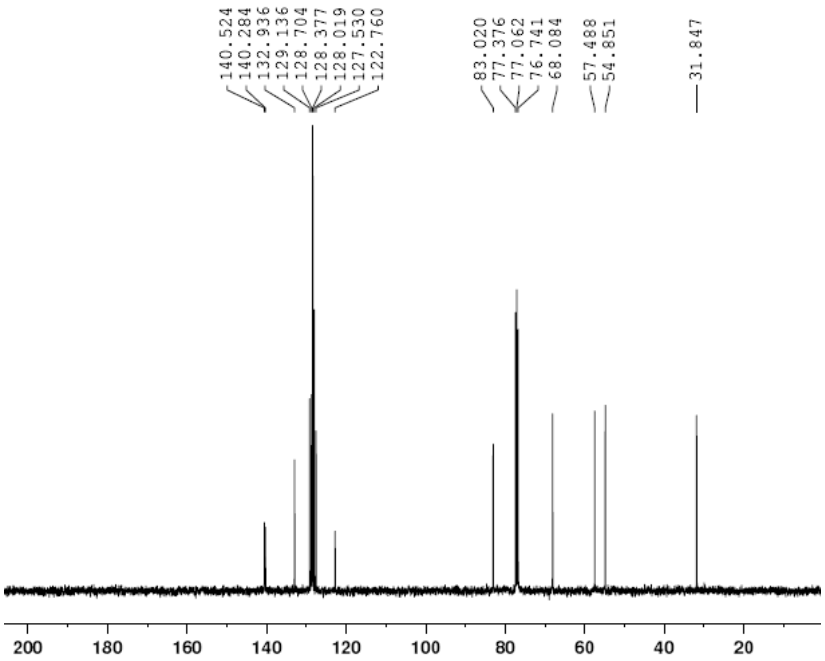
NOESY Expansion 5c



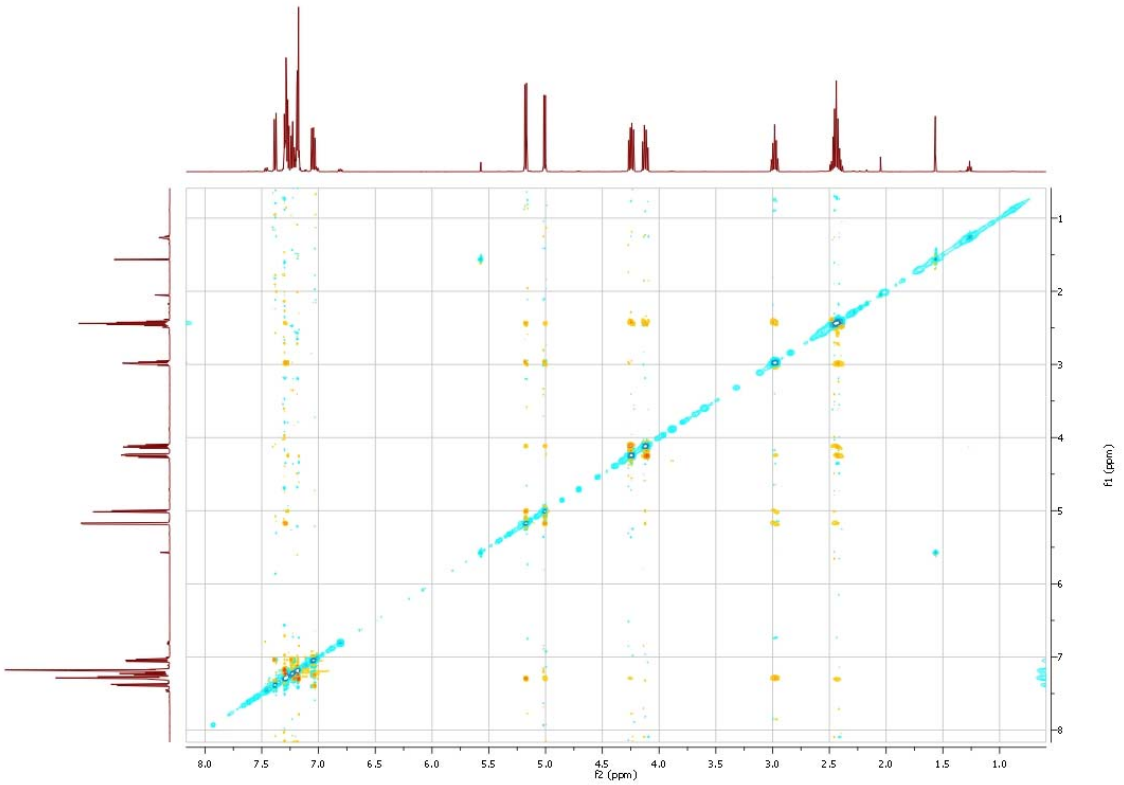
^{1}H NMR 5a



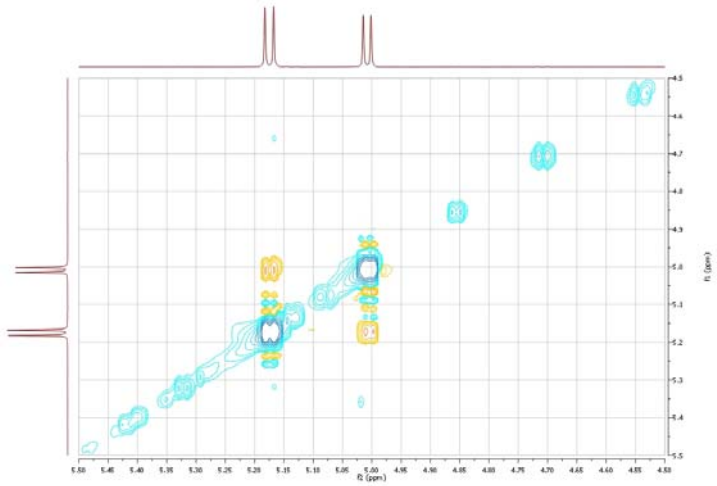
^{13}C NMR 5a



NOESY 5a

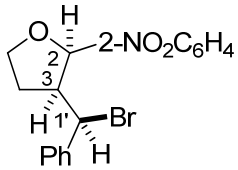


NOESY Expansion 5a



(2*R,3*S**,1'*R**)-3-[Bromo(phenyl)methyl]-2-(2-nitrophenyl)tetrahydrofuran 6c**

(Table 2, entry 5)



6c
(2,3-*cis*)

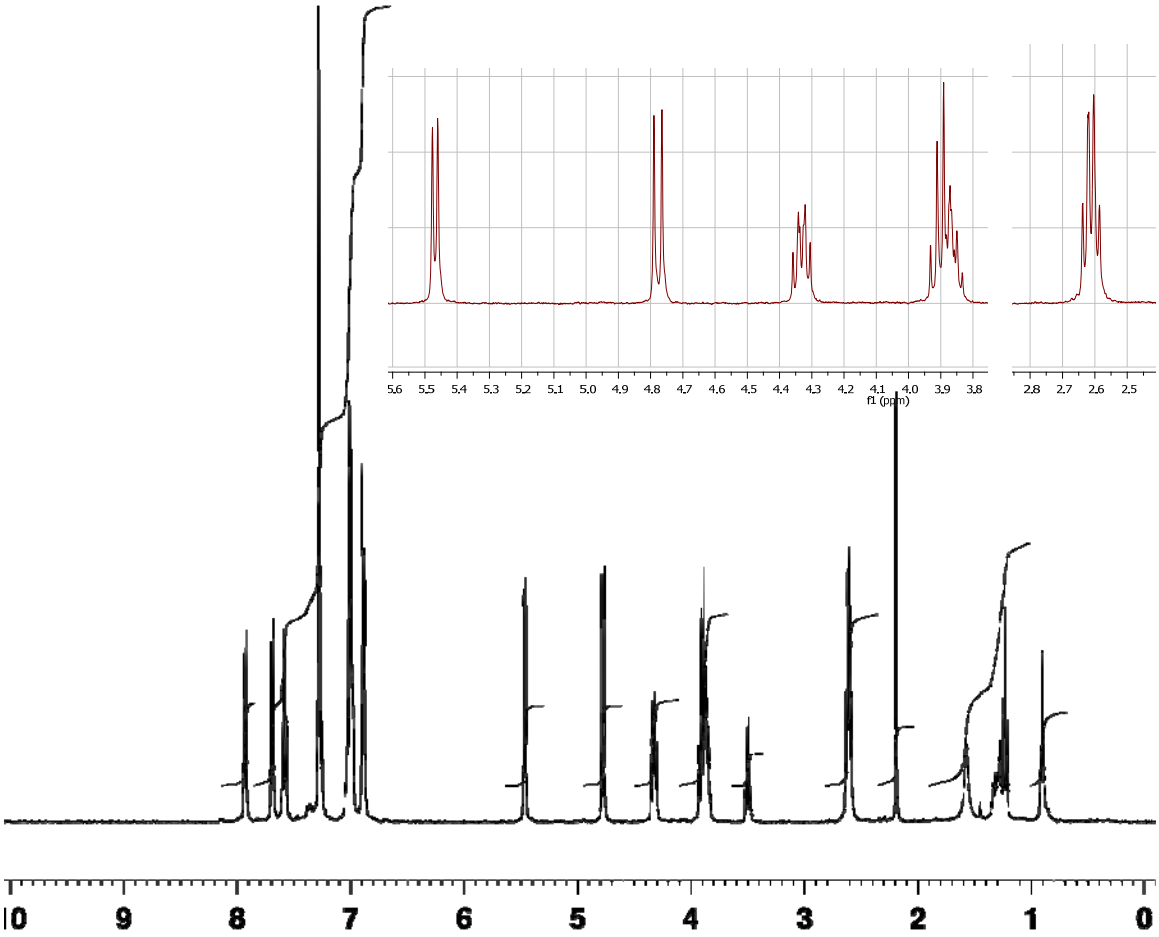
Chemical Formula: $C_{17}H_{16}BrNO_3$
Exact Mass: 361.03
Molecular Weight: 362.22

Using the general procedure, *(E)*-4-phenylbut-3-en-1-ol (90 mg, 0.6 mmol) and 2-nitrobenzaldehyde (90 mg, 0.6 mmol) after 2.5 h, purifying by FC eluting with EtOAc:Pet Ether (1:20), yielded the THF **6a** as an off-white solid (270 mg, 83% yield). m.p. 81-82 °C; υ_{max} ($CHCl_3$): 1612, 1579 (NO_2), 1521, 1454, 1339, 1243 (C-O), 1193, 1060 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400MHz): 2.60 (2H, m, OCH_2CH_2), 3.85 (1H, m, OCH_2CH_2CH), 3.89 (1H, m OCH_2), 4.33 (1H, m, OCH_2), 4.78 (1H, d, OCH(Ph-NO_2, *J* = 6.4 Hz), 5.47 (1H, d, -CH(Br)(Ph), *J* = 6.4Hz), 6.88-7.03 (5H, m, Ph(*H*)), 7.27 (1H, d, *o*-$(NO_2)C_6H_4$(*H*), *J* = 7.2, 6.8 Hz), 7.58 (1H, dd, *o*-$(NO_2)C_6H_4$(*H*), *J* = 7.6, 7.2 Hz), 7.69 (1H, d, *o*-$(NO_2)C_6H_4$(*H*), *J* = 7.6 Hz), 7.93 (1H, d, *o*-$(NO_2)C_6H_4$(*H*), *J* = 7.6 Hz); **^{13}C NMR** ($CDCl_3$, 100MHz): 34.1 (t), 48.3 (t), 58.2 (d), 66.6 (d), 79.1 (d), 124.9 (d), 127.1 (d), 127.6 (2 × d), 128.2 (2 × d), 128.3 (d), 129.4 (d), 133.3 (d), 134.7 (s), 140.8 (s), 146.9 (s); *m/z* (CI): 379/381 (MNH_4^+, 30%) 299 (30), 282 (20), 270 (25), 248 (100); Found: *m/z* (CI) MNH_4^+ 379.0652, $C_{17}H_{20}N_2O_3{}^{79}Br$ requires 379.0657 (Δ=-1.4 ppm). A single crystal X-ray structure determination was performed on this product (see Separate Supporting Information File).

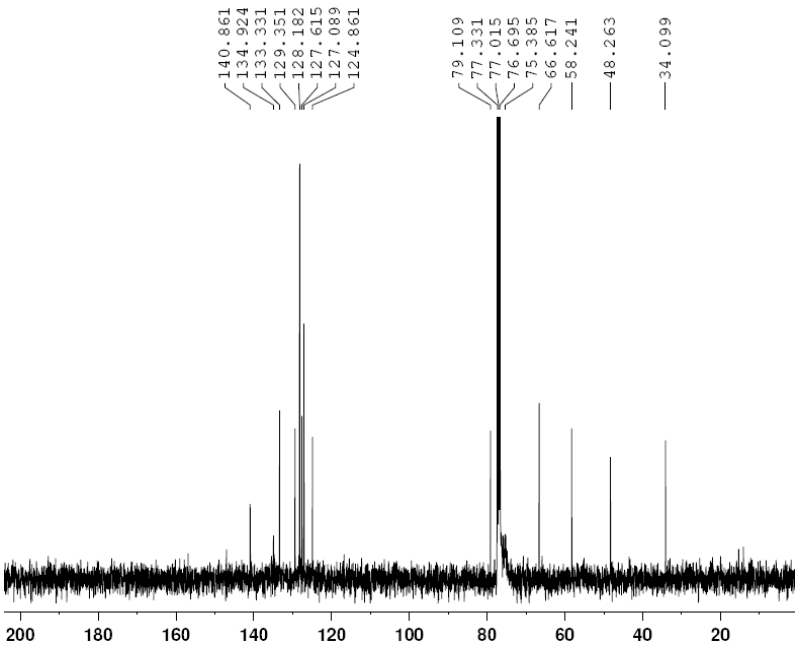
NOE Table

6c	
	4.78 ppm (H-2)
5.47 ppm (H-1')	×

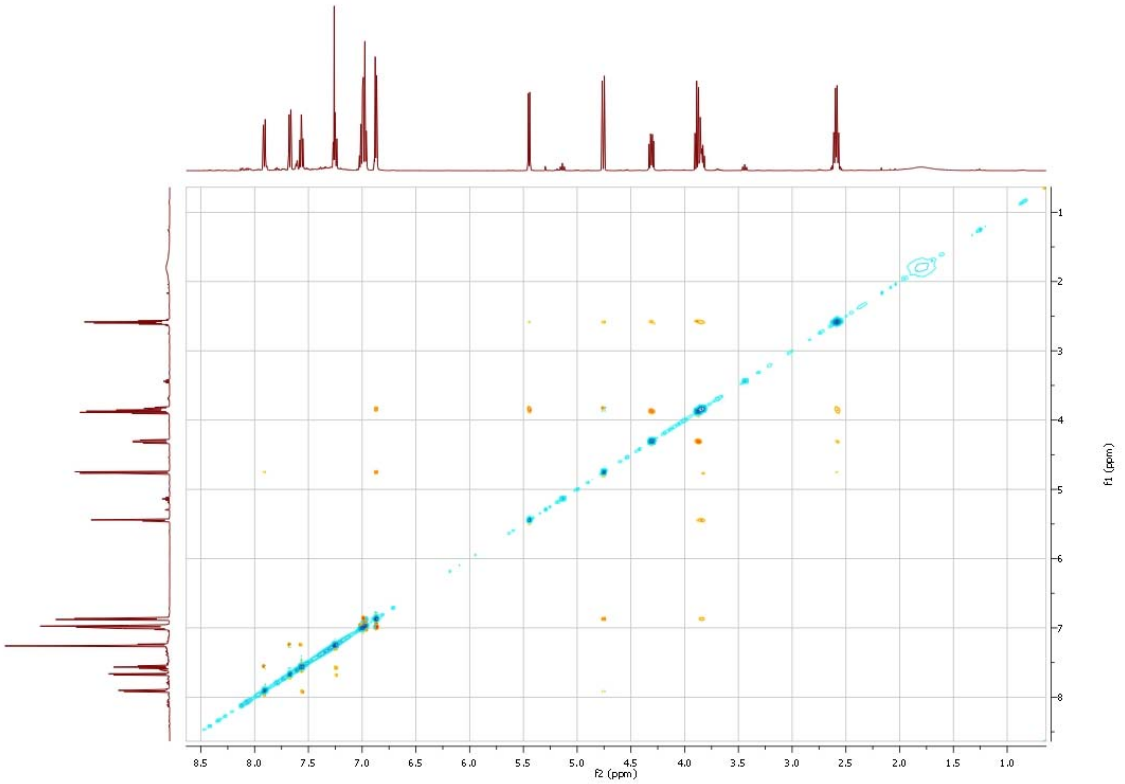
^{1}HNMR 6c



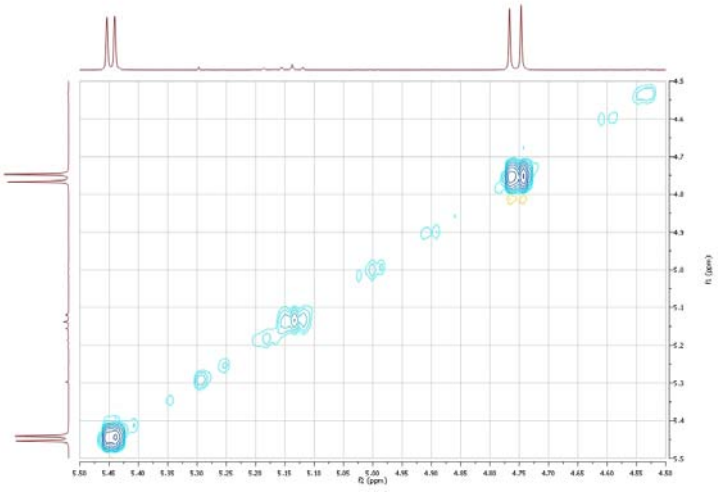
^{13}C NMR 6c



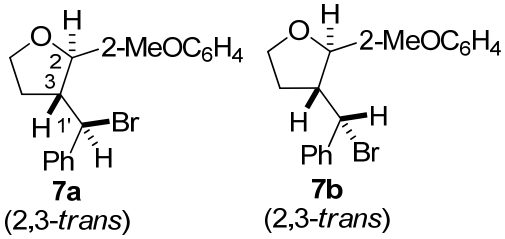
NOESY 6c



NOESY Expansion 6c



3-[Bromo(phenyl)methyl]-2-(2-methoxyphenyl)tetrahydrofuran 7 (Table 2, entry 6)



Chemical Formula: $C_{18}H_{19}BrO_2$
Exact Mass: 346.06
Molecular Weight: 347.25

Using the general procedure, *(E)*-4-phenylbut-3-en-1-ol (100 mg, 0.67 mmol) and 2-methoxybenzaldehyde (90 mg, 0.67 mmol) after 4 h, yielded a thick pale yellow oil comprising THF **7** as a mixture of two diastereomers (**7a**:**7b**, 87:13 by ^{1}H NMR integration). The major isomer was purified by FC eluting with EtOAc:Petrol ether (1:20) to give:

(2*R**,3*R**,1'*R**)-*THF* **7a** as a white solid (135 mg, 58% yield). m.p. 64-65 °C; υ_{max} (CH_2Cl_2): 2938, 2877, 1602 (C=C_{Ar}), 1589, 1489, 1453, 1243 (C-O), 1050, 1027, 751 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400MHz): 2.33 (1H, m, OCH_2CH_2), 2.41 (1H, m, OCH_2CH_2), 3.02 (1H, m, OCH(*o*-(OMe)C_6H_4-)C*H*), 3.65 (3H, s, OCH_3), 4.13 (1H, m, OCH_2), 4.23 (1H, m, OCH_2), 4.91 (1H, d, C*H*PhBr, *J* = 5.2 Hz), 5.15 (1H, d, OC*H*(C_6H_4-OMe), *J* = 8.4 Hz) 6.72 (1H, d, CH_{Ar}, *J* = 8.4 Hz), 6.87 (1H, t, CH_{Ar}, *J* = 7.2 Hz), 7.16-7.28 (5H, m, CH_{Ar}), 7.34 (2H, m, CH_{Ar}); **^{13}C NMR** ($CDCl_3$, 100MHz): 31.5 (t), 54.0 (t), 54.9 (d), 58.5 (d), 67.7 (d), 79.3 (d), 110.2 (s), 120.5 (d), 127.1 (d), 128.1(d), 128.2 (d), 128.5 (d), 129.9 (d), 141.0 (d), 156.3 (s); *m/z* (CI): 364/366 (MNH_4^+, 55%) 299 (12), 286 (30), 267 (100), 197 (30); Found: *m/z* (CI) MNH_4^+ 364.0910 $C_{18}H_{23}NO_2{}^{79}Br$ requires 364.0912 (Δ=-0.6 ppm).

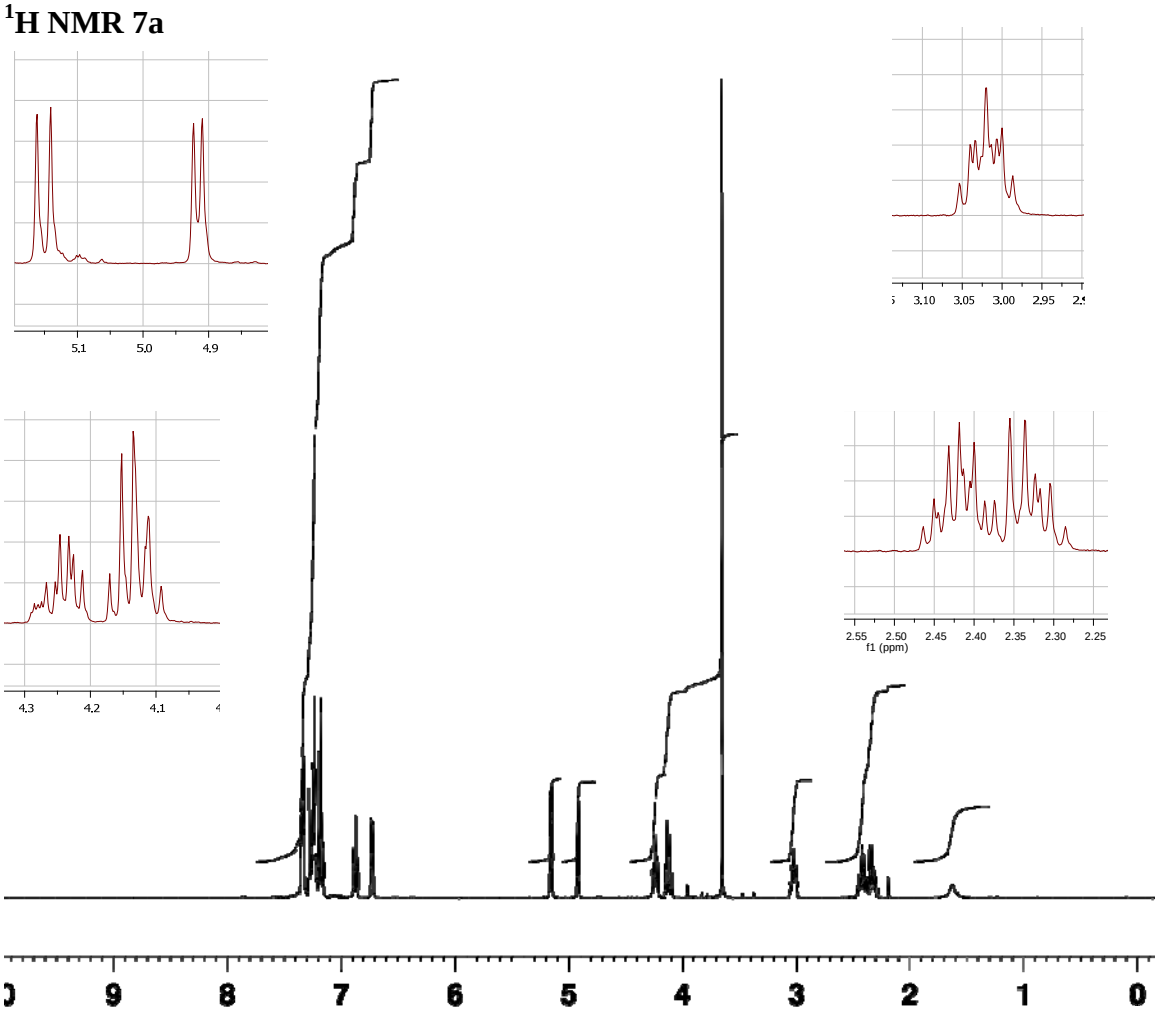
NOE Table

7a	
	5.15 ppm (H-2)
4.91 ppm (H-1')	✓

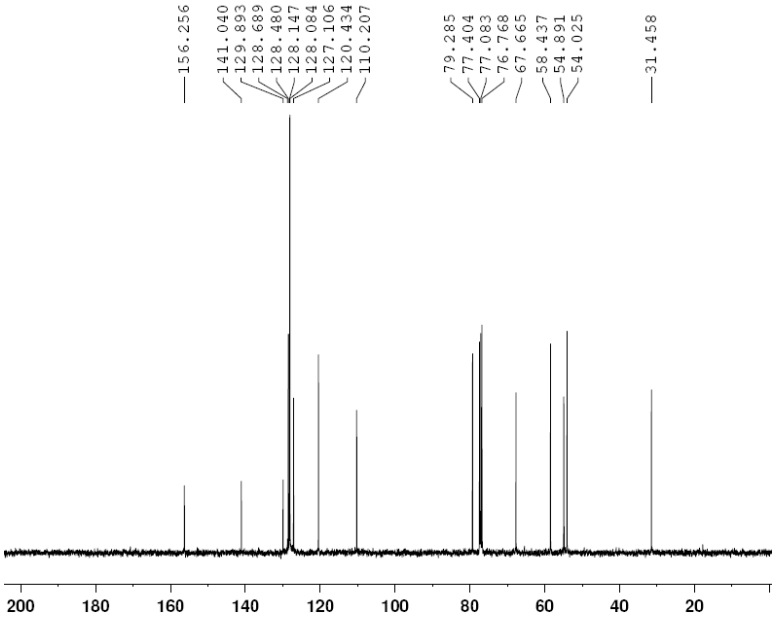
(2*R**,3*S**,1'*S**)-*THF* **7b**: **^{1}H NMR** ($CDCl_3$, 400MHz) - distinguishable/diagnostic peaks only: 2.50 (2H, m, OCH_2CH_2), 3.37 (3H, s, OCH_3), 3.58 (1H, m, OCH(*o*-(OMe)C_6H_4-

)C*H*), 3.90 (1H, m, OCH_2), 4.30 (1H, m, 4.72 (1H, d, -C*H*$_2$) OC*H*(*o*-(OMe)C_6H_4-), *J* = 10.4 Hz), 5.20 (1H, d, C*H*(Ph)(Br), *J* = 6.8 Hz).

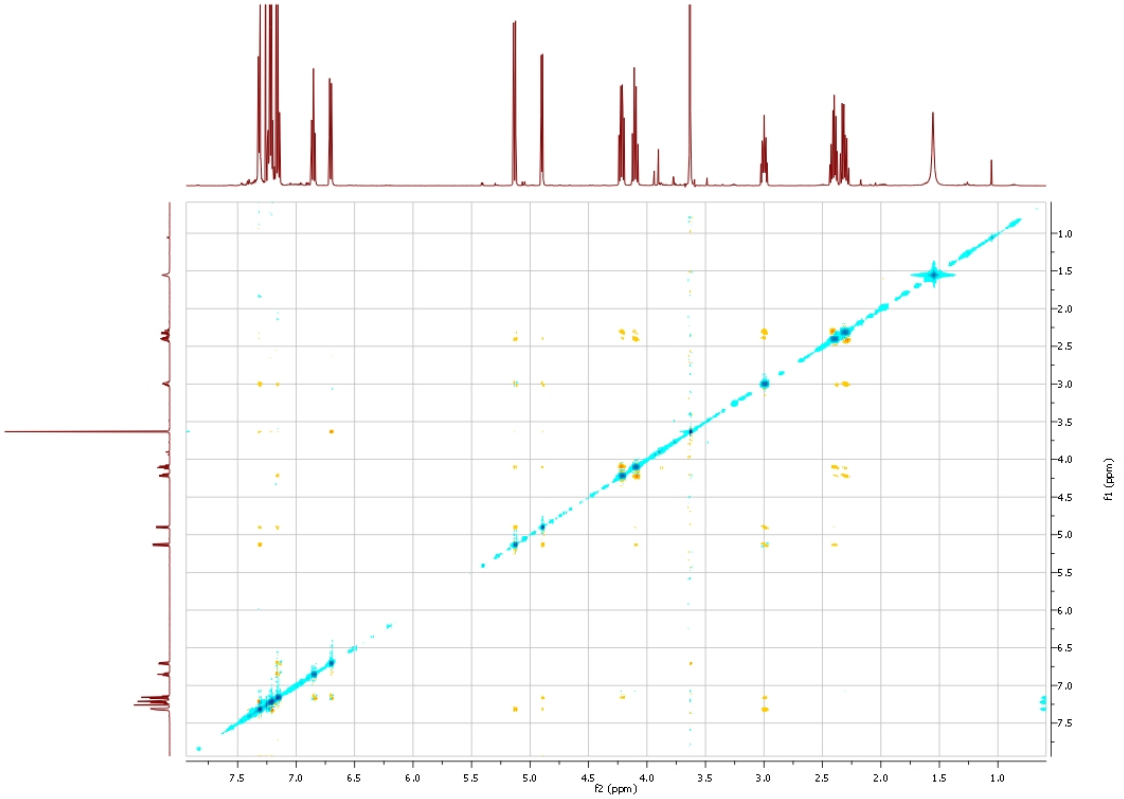
^{1}H NMR 7a



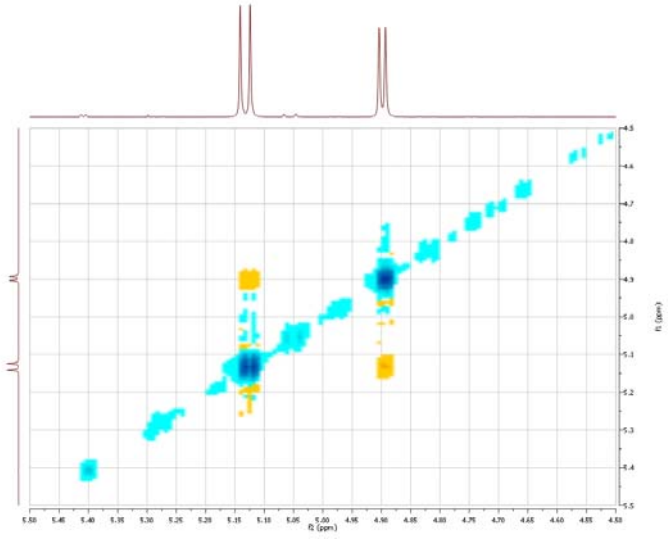
^{13}C NMR 7a



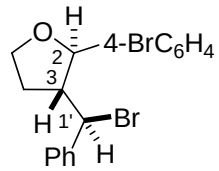
NOESY 7a



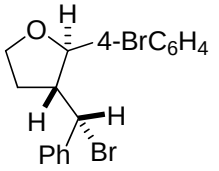
NOESY Expansion 7a



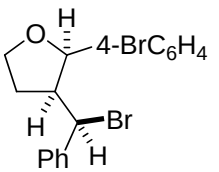
3-[Bromo(phenyl)methyl]-2-(4-bromophenyl)tetrahydrofuran 8 (Table 2, entry 7)



8a
(2,3-*trans*)



8b
(2,3-*trans*)



8c
(2,3-*cis*)

Chemical Formula: $C_{17}H_{16}Br_2O$
Exact Mass: 393.96
Molecular Weight: 396.12

Using the general procedure, *(E)*-4-phenylbut-3-en-1-ol (100 mg, 0.67 mmol) and 4-Bromobenzaldehyde (140 mg, 0.67 mmol) after 2 h, purifying by FC eluting with EtOAc:Pet Ether (1:20) yielded the THF **8** as a yellow oil (145 mg, 55% yield) comprising an inseparable mixture of three diastereoisomers (**8a**:**8b**:**8c**, 68:20:12 by ^{1}H NMR integration). υ_{max} (CH_2Cl_2): 2947, 2874, 1734, 1591, 1486, 1455, 1275, 1243, 1066, 1007 cm^{-1}; *m/z* (CI): 412/414/416/418 (MNH_4^+, 70%) 334 (30), 317 (100); Found: *m/z* (CI) MNH_4^+ 411.9896 $C_{17}H_{20}NO^{79}Br_2$ requires 411.9912 (Δ=-3.8 ppm).

(2*R**,3*R**,1'*R**)-*THF* **8a**: **^{1}H NMR** ($CDCl_3$, 400MHz): 2.37 (2H, m, OCH_2CH_2) 2.83 (1H, m, $OCH(C_6H_4Br)CH$) 4.07 (1H, m, OCH_2) 4.19 (1H, m, OCH_2) 4.48 (1H, d, CH(Br)(Ph), *J* = 6.4 Hz), 4.97 (1H, d, CHPh, *J* = 8.4 Hz), 6.88 (2H, d, CH_{Ar}, *J* = 8.4 Hz), 7.30-7.41 (5H, m, CH_{Ar}) 7.51 (2H, d, CH_{Ar}, *J* = 8.4 Hz); **^{13}C NMR** ($CDCl_3$, 100MHz): 31.8 (t), 56.2 (t), 57.0 (d), 67.6 (d), 83.3 (d), 125.9 (s), 127.1 (d), 127.4 (d), 127.8 (2 × d), 128.5 (d), 128.6 (2 × d), 128.9 (2 × d), 131.3 (s), 140.6 (s).

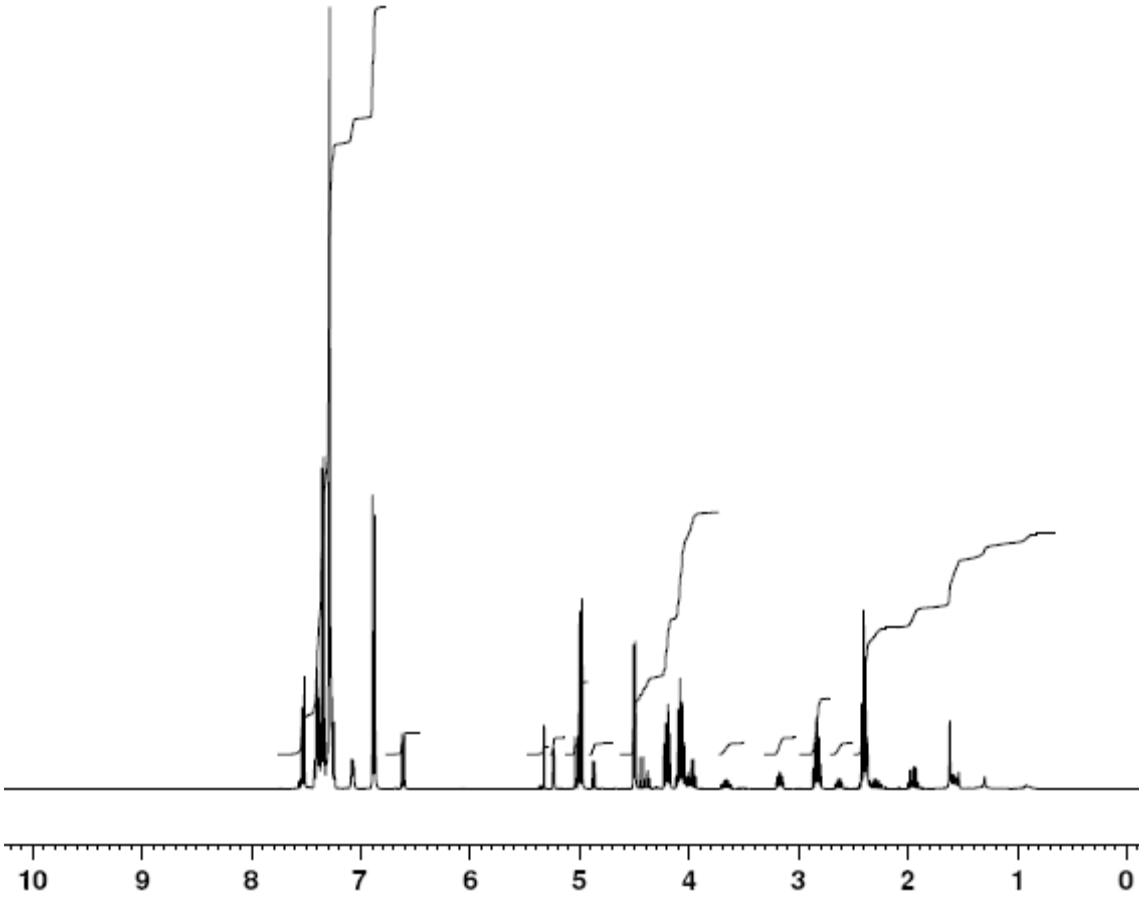
(2*R**,3*R**,1'*S**)-*THF* **8b**: **^{1}H NMR** ($CDCl_3$, 400MHz) - distinguishable/diagnostic peaks only: 1.55 (1H, m, OCH_2CH_2), 2.00 (1H, m, OCH_2CH_2), 3.32 (1H, m, $OCH(C_6H_4Br)CH$), 3.95 (1H, m, OCH_2), 4.05 (1H, m, OCH_2), 5.01 (1H, d, CH(Br)(Ph), *J* = 11.2 Hz), 5.22 (1H, d, CHPh, *J* = 3.6 Hz), 6.62 (1H, d, CH_{Ar}, *J* = 8.3).

(2*R**,3*S**,1'*R**)-*THF* **8c**: **^{1}H NMR** ($CDCl_3$, 400MHz) - distinguishable/diagnostic peaks only: 3.63 (1H, m, $OCH(C_6H_4Br)CH$), 4.42 (1H, d, CH(Br)(Ph), *J* = 11.6 Hz), 4.86 (1H, d, CHPh, *J* = 8 Hz).

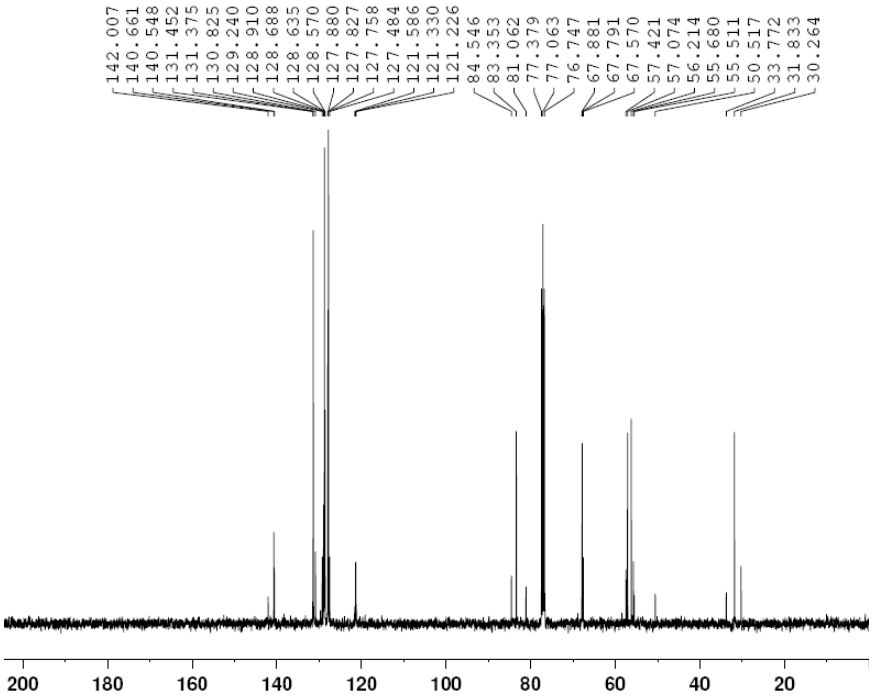
NOE Table

8a		**8b**		**8c**	
	4.97 ppm (H-2)		5.22 ppm (H-2)		4.86 ppm (H-2)
4.48 ppm (H-1')	✓	5.01 ppm (H-1')	✓	4.42 ppm (H-1')	✖

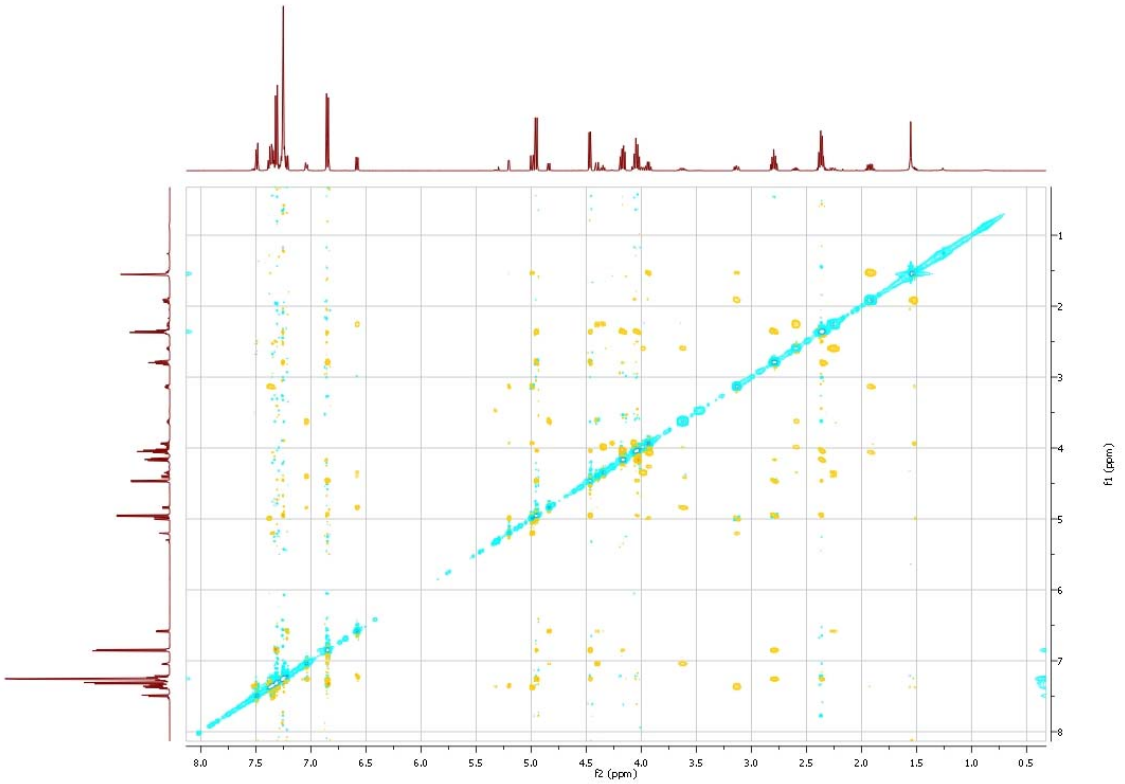
^{1}H NMR (8a:8b:8c, 68:20:12)



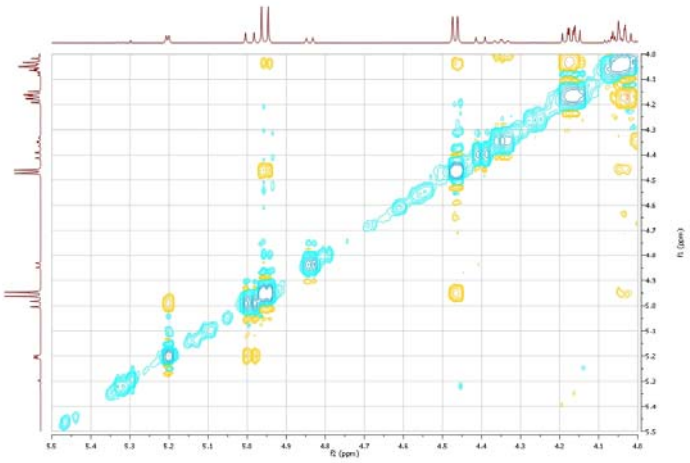
^{13}C NMR (8a:8b:8c, 68:20:12)



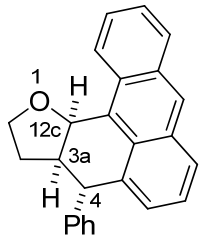
NOESY (8a:8b:8c, 68:20:12)



NOESY Expansion (8a:8b:8c, 68:20:12)



(12c*R,3a*R**, 4*S**)-1-Oxa-4-phenyl-1,2,3,3a,4,12c-hexahydroindeno[6,5,4-*de*]anthracene 9** (Scheme 3)

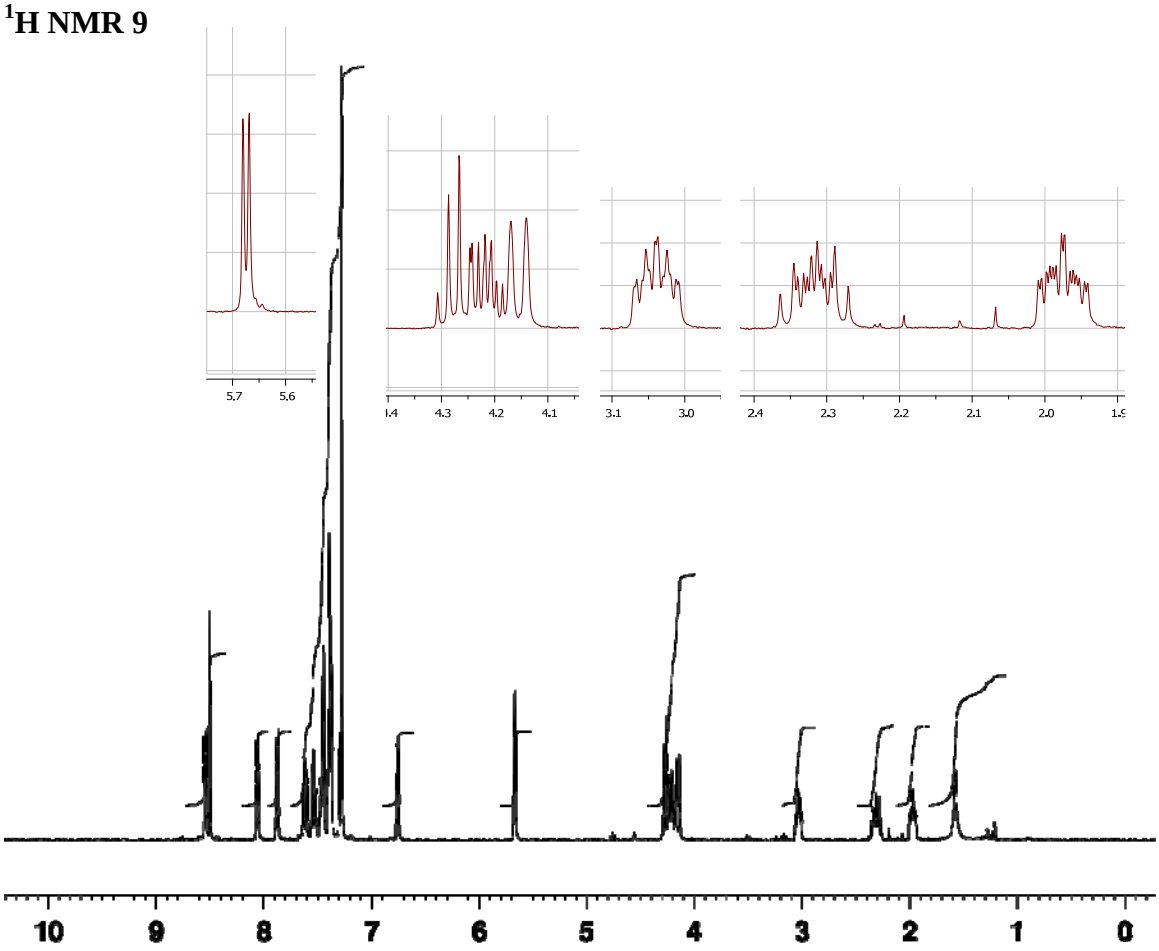


9

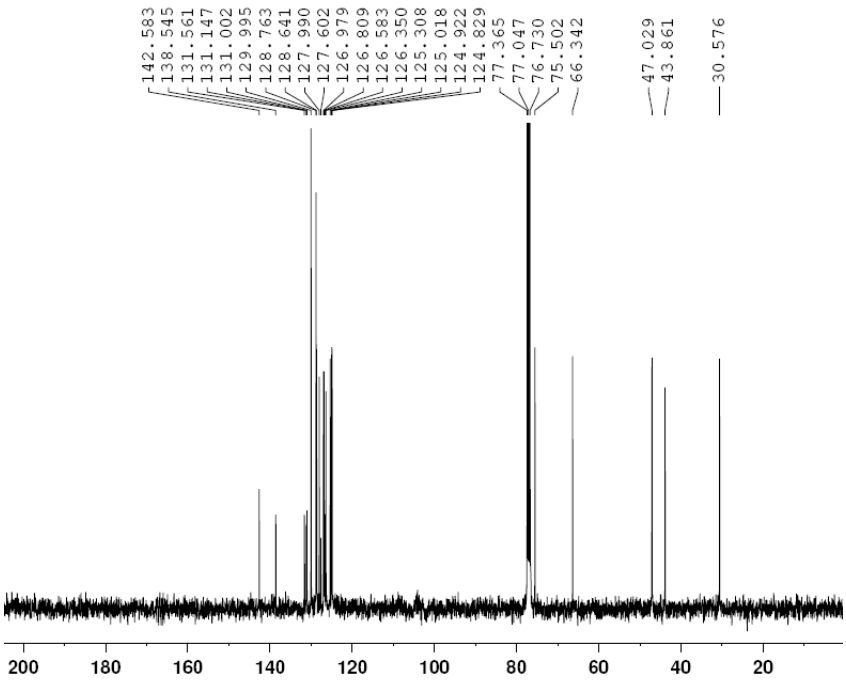
Chemical Formula: $C_{25}H_{20}O$
Exact Mass: 336.15
Molecular Weight: 336.43

Using the general procedure, *(E)*-4-phenylbut-3-en-1-ol (120 mg, 0.81 mmol) and 9-anthraldehyde (167 mg, 0.81 mmol) after 7 h, yielded the fused pentacycle **9** as a pale yellow solid after recrystallisation using Petrol Ether and Ethyl acetate (250 mg, 92% yield). m.p. 181-182 °C; υ_{max} (CH_2Cl_2): 3057, 3030, 2873, 1625, 1603, 1498, 1452, 1302, 1268, 1091, 1031, 737 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400MHz): 1.98 (1H, dddd, OCH_2CH_2, *J* = 12, 6.4, 4.8, 1.6 Hz), 2.32 (1H, dddd, OCH_2CH_2, *J* = 10, 7.6, 3.2, 2 Hz), 3.04 (1H, m, OCH(anthr)C*H*,), 4.15 (1H, d, CH, *J* = 11.6 Hz), 4.20 (1H, m, OCH_2), 4.27 (1H, m, OCH_2), 5.67 (1H, d, CH, *J* = 4.8 Hz), 6.76 (1H, d, CH_{anthr}, *J* = 7.2 Hz), 7.28 (1H, m, CH_{anthr}), 7.39 (3H, m, CH_{Ph}), 7.46 (2H, m, CH_{Ph}), 7.53 (1H, m, CH_{anthr}), 7.62 (1H, m, CH_{anthr}), 7.87 (1H, d, CH_{anthr}, *J* = 8.4 Hz), 8.06 (1H, d, CH_{anthr}, *J* = 8.4 Hz), 8.50 (1H, s, CH_{anthr}), 8.54 (1H, d, CH_{anthr}, *J* = 8.8 Hz); **^{13}C NMR** ($CDCl_3$, 100MHz): 30.6 (t), 43.9 (t), 47.0 (d), 66.3 (d), 75.5 (d), 124.8 (s), 124.9 (s), 125.0 (d), 125.3 (d), 126.3 (d), 126.8 (d), 127.0 (d), 127.6 (2 × d), 128.0 (2 × d), 128.6 (2 × d), 128.8 (d), 130.0 (s), 131.0 (s), 131.1 (s), 131.6 (s), 138.5 (s), 142.6 (s); *m/z* (CI): 337 (MH^+, 100%), 207 (30), 168 (30); Found: *m/z* (CI) MH^+ 337.1585 $C_{25}H_{21}O$ requires 337.1592 (Δ=-2.2 ppm). A single crystal X-ray structure determination was performed on this product (see Separate Supporting Information File).

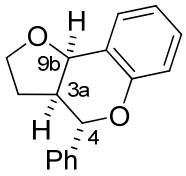
^{1}H NMR 9



^{13}C NMR 9



(3a*S,4*S**,9b*R**)-4-Phenyl-3,3a,4,9b-tetrahydro-2H-furo[3,2-c]chromene 10** (Scheme 4)

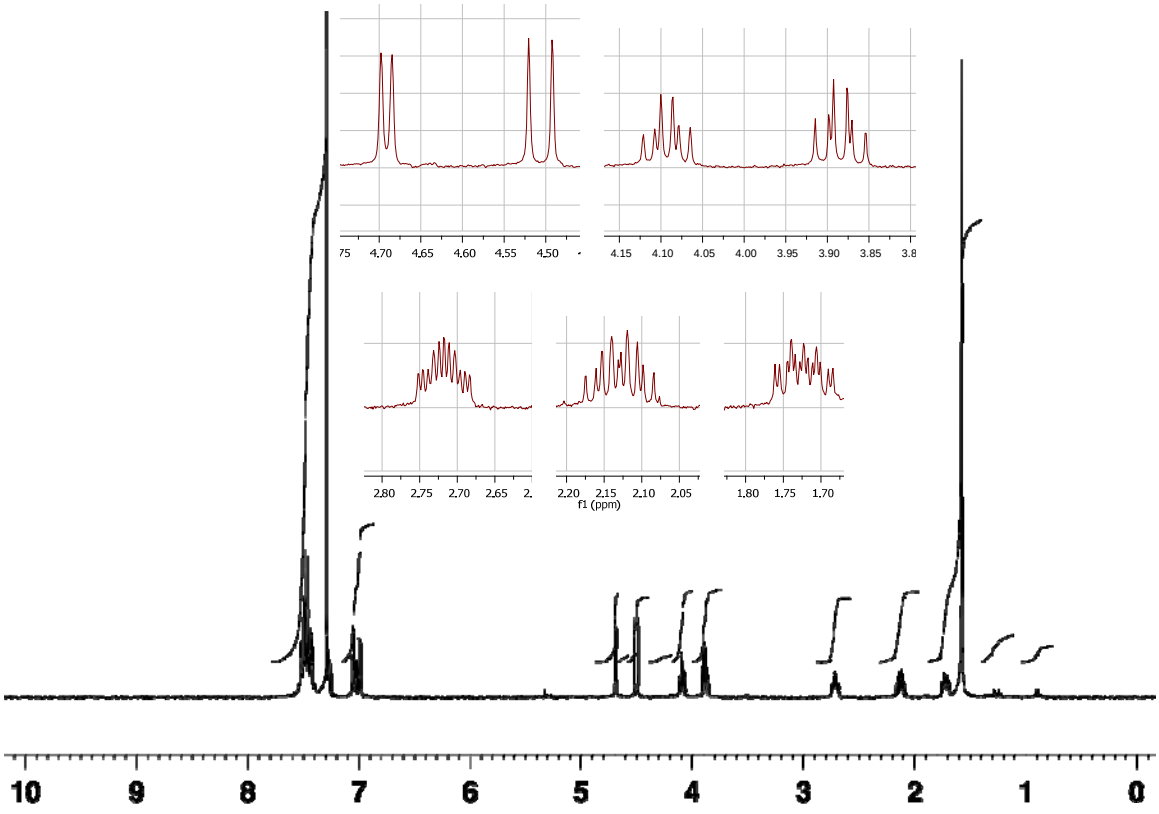


Chemical Formula: $C_{17}H_{16}O_2$
Exact Mass: 252.12
Molecular Weight: 252.31

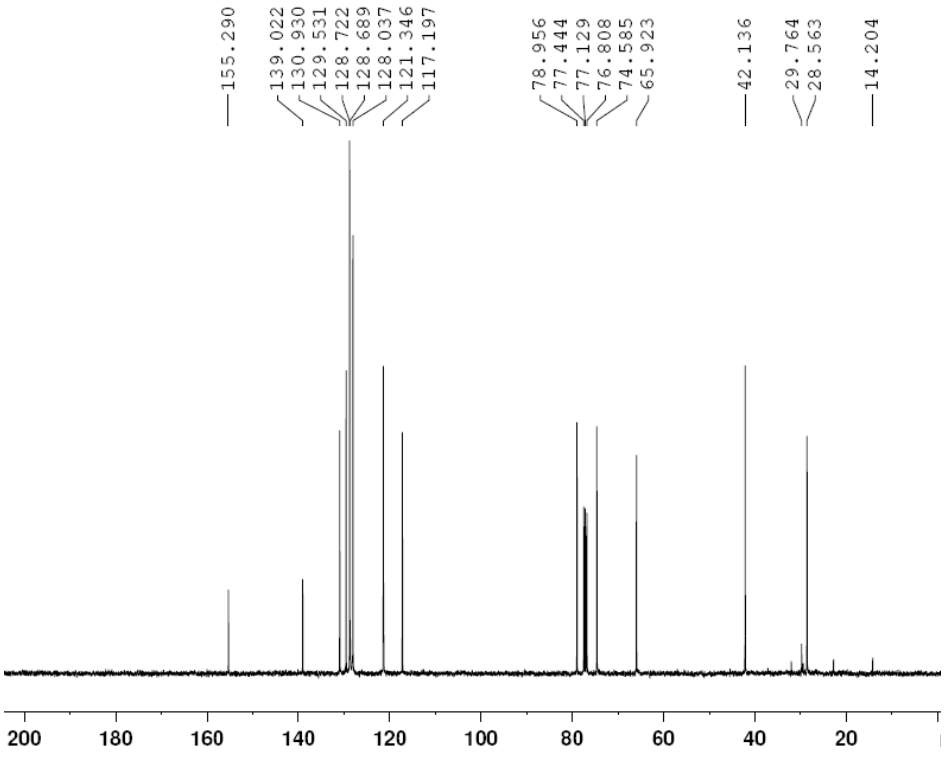
10

Using the general procedure but substituting the combination of tin(IV) bromide and TMS-Br with just tin(IV) chloride and performing the reaction at rt, *(E)*-4-phenylbut-3-en-1-ol (100 mg, 0.67 mmol) and 2-hydroxybenzaldehyde (81 mg, 0.67 mmol) after 4 h, yielded the furano[3,2-c]benzopyran **10** as a white solid (150 mg, 88% yield). m.p. 94-95 °C; υ_{max} (CH_2Cl_2): 2958, 2927, 2858, 1611, 1583, 1485, 1453, 1362, 1247 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400MHz): 1.72 (1H, m, OCH_2CH_2), 2.12 (1H, m, OCH_2CH_2), 2.72 (1H, m, $OCH(C_6H_4)CH$,), 3.89 (1H, m, OCH_2), 4.10 (1H, m, OCH_2), 4.50 (1H, d, CH, J = 11.2 Hz), 4.69 (1H, d, CH, J = 5.2 Hz), 6.99 (1H, d, CH_{Ar}, J = 8 Hz), 7.05 (1H, td, CH_{Ar}, J = 7.6, 0.8 Hz), 7.27 (1H, m, CH_{Ar})7.42-7.52 (6H, m, CH_{Ar}); **^{13}C NMR** ($CDCl_3$, 100MHz): 28.5 (t), 42.1 (t), 65.9 (d), 74.6 (d), 78.9 (d), 117.1 (s), 121.3 (d), 126.2 (d), 128.0 (2 × d), 128.6 (2 × d), 128.7 (d), 129.5 (d), 130.9 (d), 138.9 (s), 155.2 (s); *m/z* (CI): 270 (MNH_4^+, 100%), 253 (MH^+, 30); Found: *m/z* (CI) MH^+ 253.1224, $C_{17}H_{17}O_2$ requires 253.1229 (Δ = -1.8 ppm). A single crystal X-ray structure determination was performed on this product (see Separate Supporting Information File).

^{1}H NMR 10



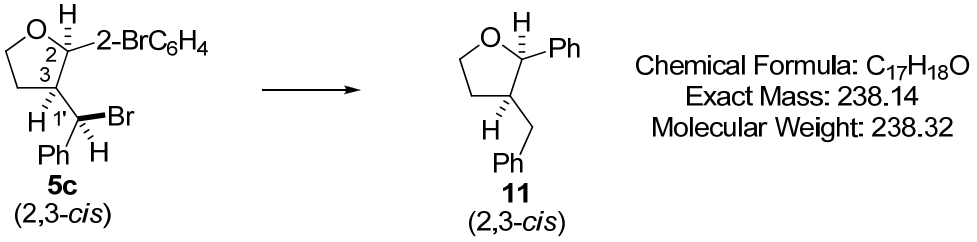
^{13}C NMR 10



General Procedure for Debromination Reactions:

The required THF substrate (0.17 mmol) and $NiCl_2 \cdot 6H_2O$ (0.34 mmol) were fully dissolved in MeOH (2.5 mL). $NaBH_4$ (1.02 mmol) was then added in a single portion and the reaction stirred at RT for 15 min before diluting with MeOH (5 mL) and filtering through Celite®. The filtrate was concentrated under reduced pressure and the resulting oil was dissolved in EtOAc (10 mL), washed with H_2O (5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude de-brominated THF product.

Di-debromination of 5c to give (2*R,3*R**)-3-[phenylmethyl]-2-(2-phenyl)tetrahydrofuran 11**



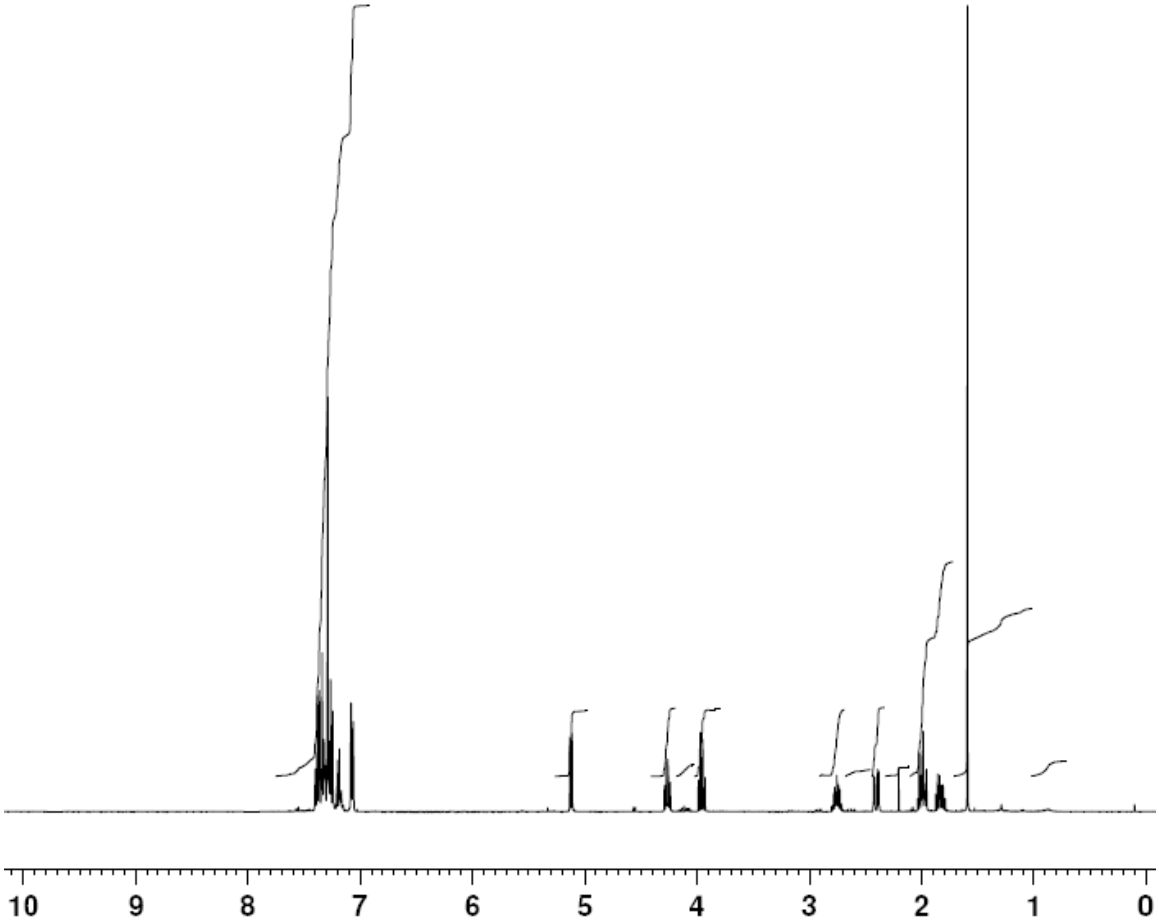
Using the general procedure, (2*R**,3*S**,1'*R**)-3-[bromo(phenyl)methyl]-2-(2-bromophenyl)tetrahydrofuran **5c** (50mg, 0.13 mmol), $NiCl_2 \cdot 6H_2O$ (60 mg, 0.25 mmol) and $NaBH_4$ (30 mg, 0.76 mmol) after 15 min, purifying by FC eluting with hexane:ethyl acetate (19:1), yielded the THF **11** as a colourless oil (3.1 mg, 10%)[2]. υ_{max} (CH_2Cl_2): 3061, 3027, 2933, 1602, 1494, 1452, 1081, 1053 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400MHz): 1.76-1.86 (1H, m, OCH_2CH_2), 1.96-2.02 (1H, m, OCH_2CH_2), 2.41 (1H, dd, C*H*Ph, 13.9-4.4), 2.76 (1H, m, OCHC*H*), 3.96 (1H, td, OCH_2, J = 8.3, 7.5 Hz), 4.27 (1H, td, OCH_2, J = 8.3, 5.1 Hz), 5.13 (1H, d, OC*H*Ph, J = 6.7 Hz), 7.06-7.41 (10H, m, CH_{Ar}). **^{13}C NMR** ($CDCl_3$, 100MHz): 30.7 (d), 36.0 (d), 45.1 (s), 67.5 (s), 83.4 (d), 125.9 (d), 126.5 (2 × d), 127.1 (d), 128.1 (2 × d), 128.3 (d), 128.8 (d), 140.6 (d), 141.0 (s); *m/z* (CI): 256 (MNH_4^+, 100%), 238 (MH^+, 10); Found: *m/z* (CI) MH^+ 239.1446, $C_{17}H_{18}O$ requires 238.1409 (Δ = 0.4 ppm).

[2] The mass balance was benzylic *mono*-debrominated product.

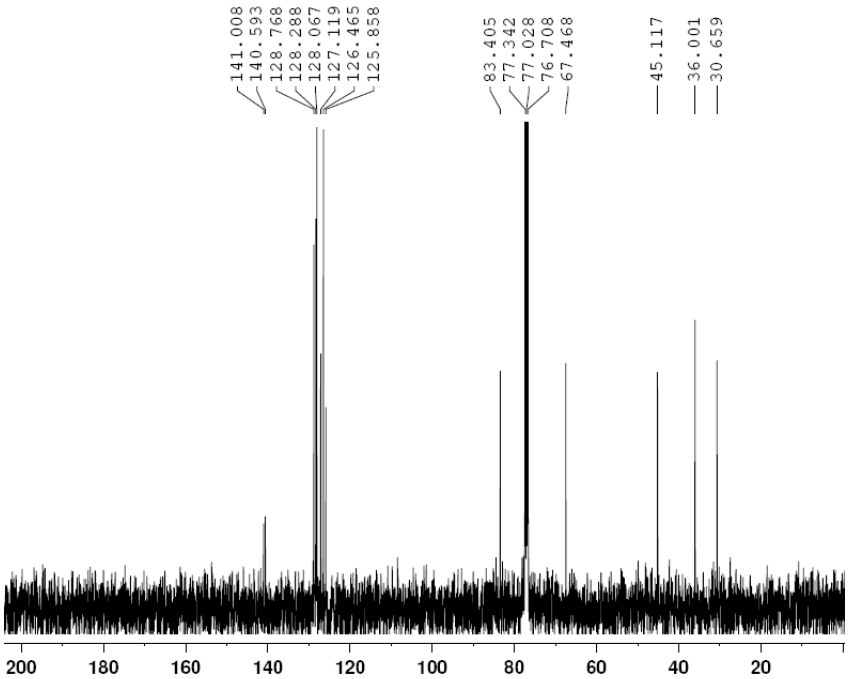
NOE Table

11	
	5.13 ppm (H-2)
2.00 ppm (H-1’)	×
5.40 ppm (H-1’)	×

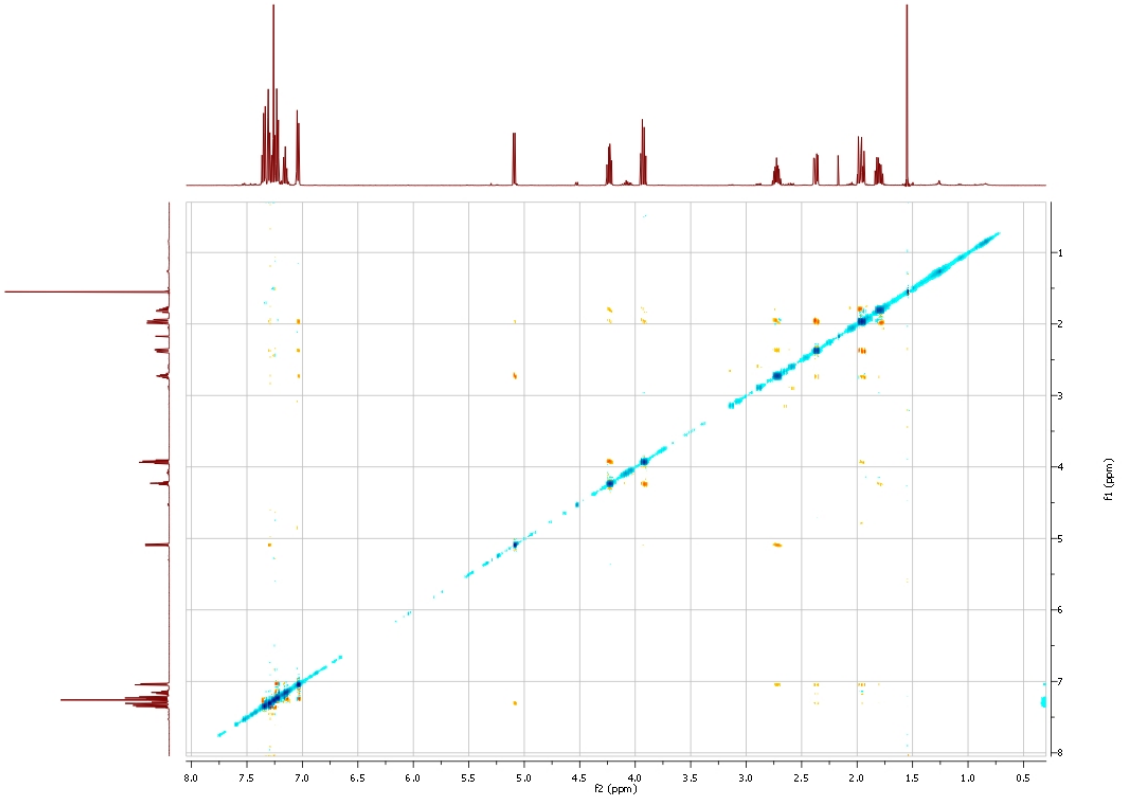
^{1}H NMR 11



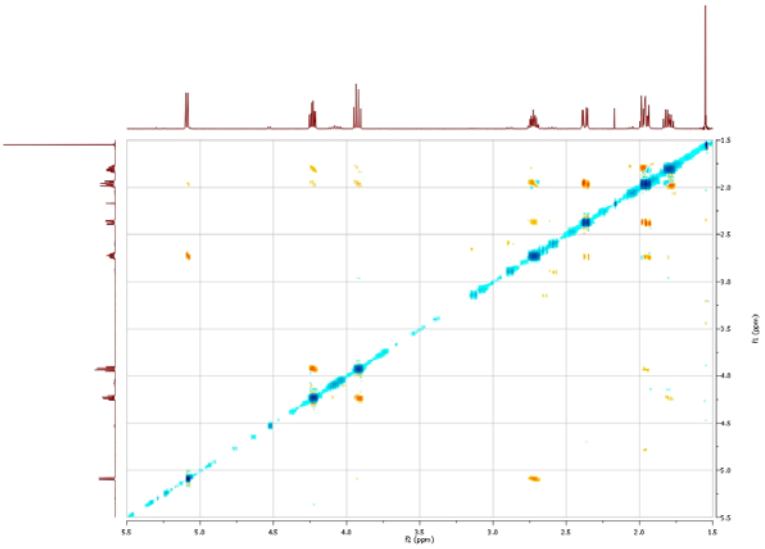
^{13}C NMR 11



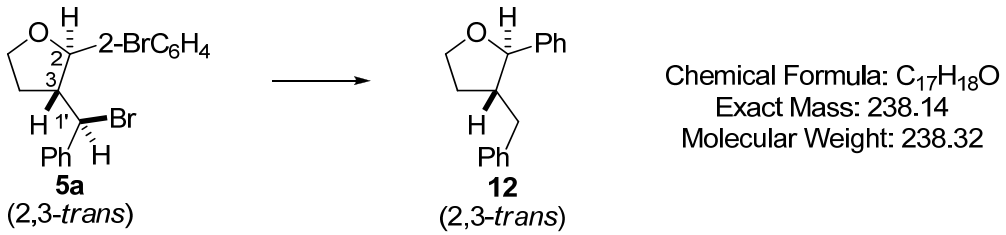
NOESY 11



NOESY Expansion 11



Didebromination of 5a to give (2*R,3*S**)-3-[phenylmethyl]-2-(2-phenyl)tetrahydrofuran 12**



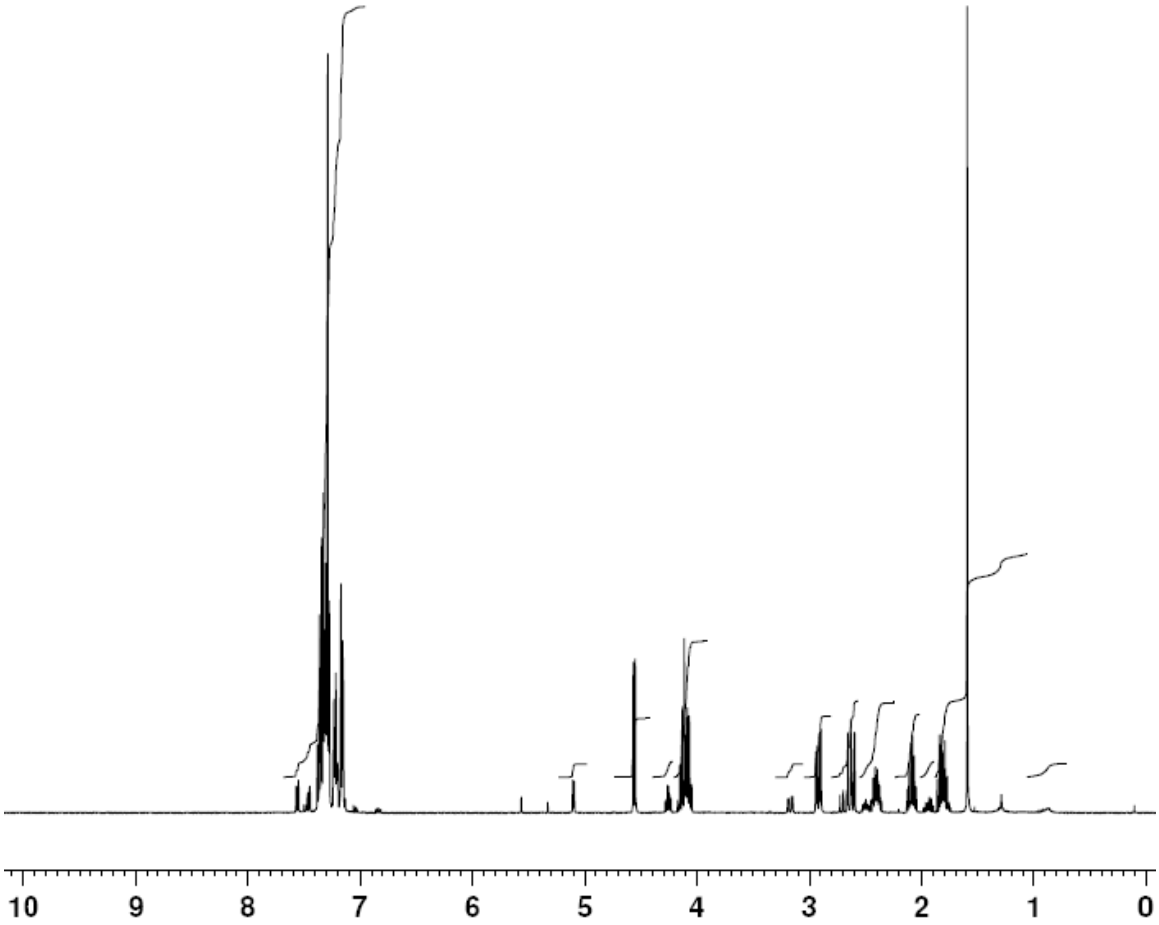
Using the general procedure, (2*R**,3*R**,1'*R**)-3-[bromo(phenyl)methyl]-2-(2-bromophenyl)tetrahydrofuran **5a** (50mg, 0.13 mmol), $NiCl_2 \cdot 6H_2O$ (60 mg, 0.25 mmol) and $NaBH_4$ (30 mg, 0.76 mmol) after 15 min, purifying by FC eluting with hexane:ethyl acetate (19:1), yielded the THF **12** as a colourless oil (4.4 mg, 13%)[3]. υ_{max} (CH_2Cl_2): 3062, 2935, 1602, 1495, 1462, 1080, 1055 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400MHz): 1.78-1.86 (1H, m, OCH_2CH_2), 2.05-2.13 (1H, m, OCH2CH2), 2.45-2.36 (1H, m, OCHCH), 2.63 (1H, dd, CH_2Ph, J = 13.5, 9.7), 2.92 (1H, dd, CH_2Ph, J = 13.5, 5.3), 4.05-4.15 (2H, m, OCH_2), 4.56 (1H, d, J = 7.3), 7.16-7.37 (10H, m, CH_{Ar}); **^{13}C NMR** ($CDCl_3$, 100MHz): 32.3 (d), 38.3 (d), 49.9 (s), 68.0 (s), 89.0 (d), 126.2 (d), 127.5 (2 × d), 128.4 (d), 128.4 (2 × d), 128.9 (2 x d), 140.4 (d); *m/z* (CI): 256 (MNH_4^+, 100%), 238 (MH^+, 10); Found: *m/z* (CI) MH^+ 239.1448, $C_{17}H_{18}O$ requires 238.1409 (Δ = 0.5 ppm).

NOE Table

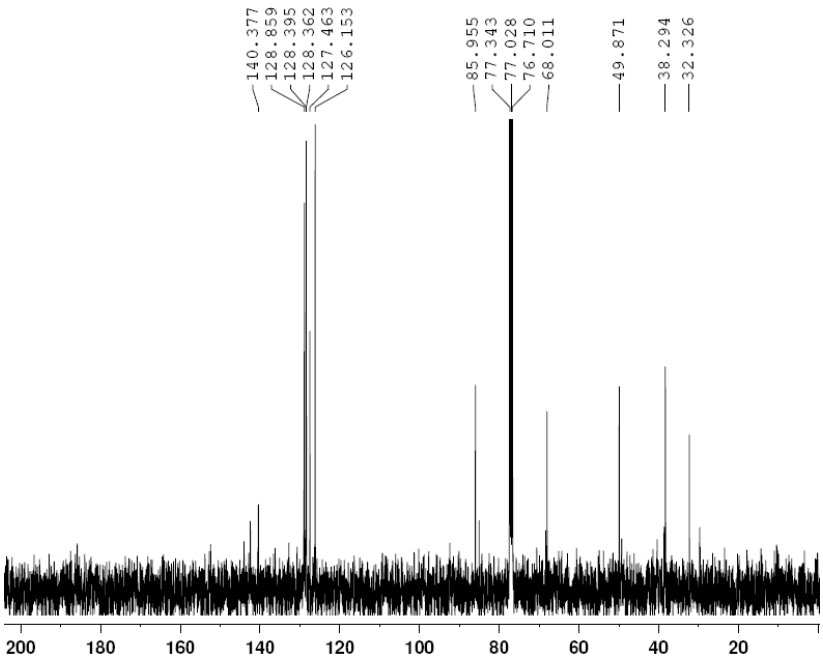
12	
	5.13 ppm (H-2)
2.63 ppm (H-1')	✓
2.92 ppm (H-1')	✓

[3] The mass balance was benzylic *mono*-debrominated product.

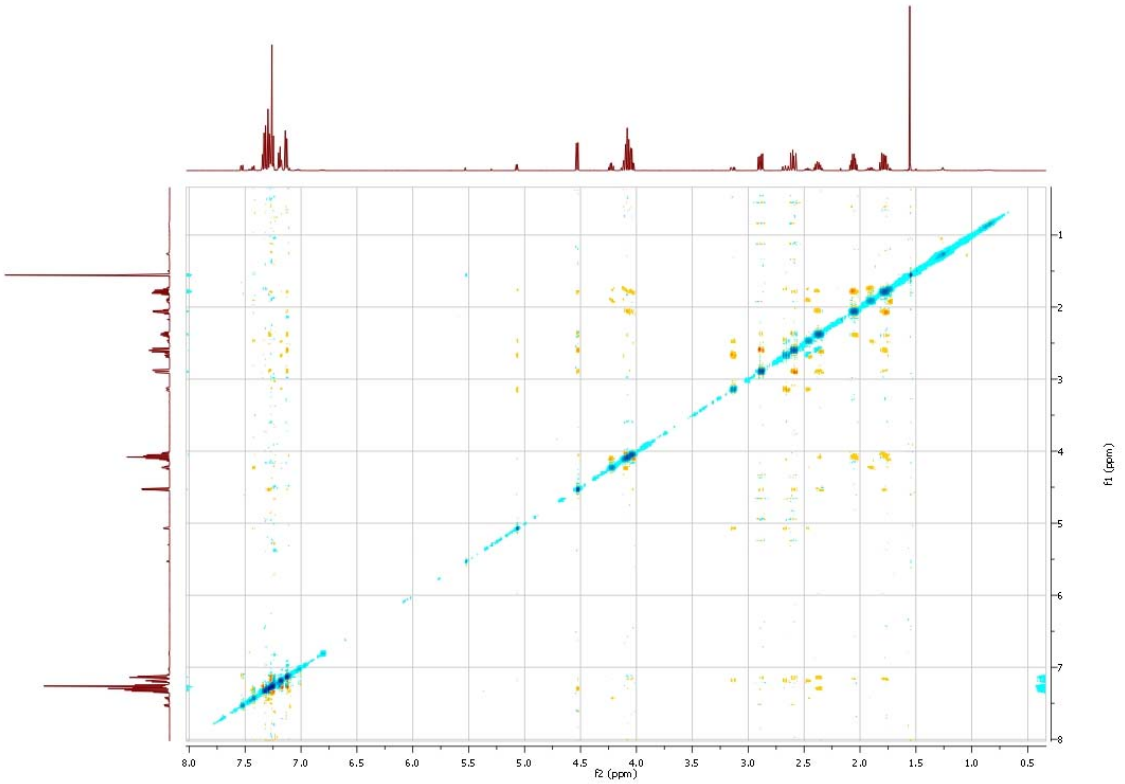
^{1}H NMR 12



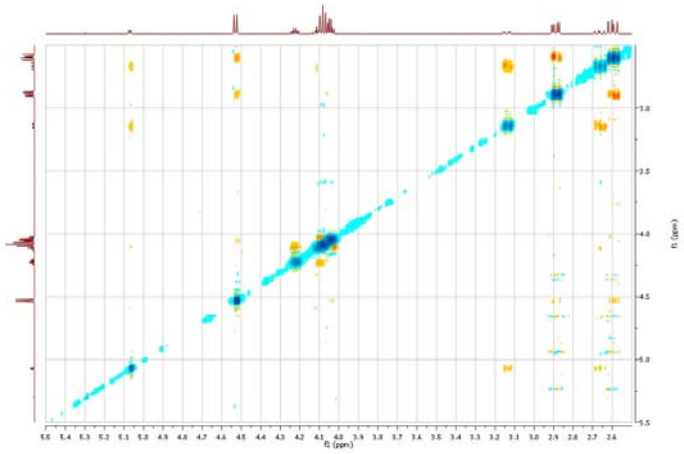
^{13}C NMR 12



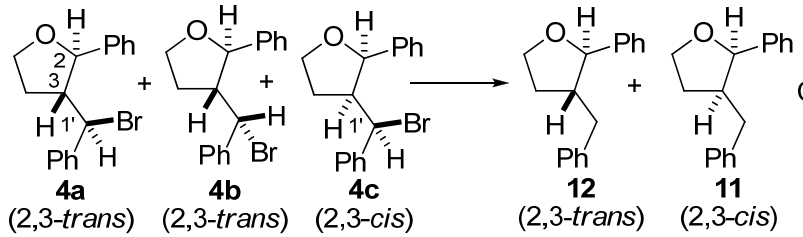
NOESY 12



NOESY Expansion 12



Mono-debromination of 4 to give 3-[phenylmethyl]-2-phenyltetrahydrofurans 11 and 12



Chemical Formula: $C_{17}H_{18}O$
Exact Mass: 238.14
Molecular Weight: 238.32

Using the general procedure, a mixture of 3-[bromo(phenyl)methyl]-2-phenyltetrahydrofurans **4** (34mg, 0.11 mmol, 77:12:11, **4a**:**4b**:**4c**), $NiCl_2 \cdot 6H_2O$ (51 mg, 0.22 mmol) and $NaBH_4$ (25 mg, 0.65 mmol) after 15 min, purifying by FC eluting with hexane:ethyl acetate (19:1), yielded a colourless oil (14.7 mg, 57% yield) comprising an inseparable mixture of two diastereomers (**12**:**11**, 84:16 by ^{1}H NMR integration). Spectroscopic data as above.

^{1}H NMR (12:11, 84:16)