Synthesis of Fused-Ring and Attached-Ring Bis-Tetrahydrofurans via Pd-Catalyzed Carboetherification

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Supporting Information

Experimental procedures and characterization data for new compounds in Tables 1–2, eq 4, and Scheme 2, complete descriptions of stereochemical assignments (128 pages).

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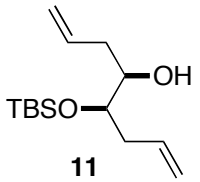
General. All reactions were carried out under a nitrogen atmosphere in oven or flame dried glassware. Tris(dibenzylideneacetone)dipalladium (0) and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. All aryl bromides and 1,3 butadiene diepoxide were obtained from commercial sources (Aldrich Chemical CO or Acros Chemical CO) and were used as obtained. (4*R*,5*S*,6*S*,7*R*)-4,7-bis(benzyloxy)deca-1,9-diene-5,6-diol,[1,2] (5*R**,6*R**)-deca-1,9-diene-5,6-diol,[3] (+)-(5*R*,6*R*)-deca-1,9-diene-5,6-diol,[4] and (4*R**,5*R**)-octa-1,7-diene-4,5-diol[5] were prepared according to literature procedures. Toluene and THF were purified using a GlassContour solvent purification system. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR. The yields reported in the

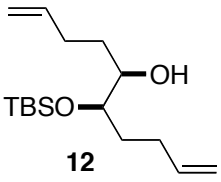
supporting information describe the result of a single experiment, whereas the yields reported in Tables 1 and 2 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Tables 1 and 2.

Preparation of Substrates



11

(±)-(4*R,5*R**)-5-(*tert*-Butyldimethylsiloxy)octa-1,7-dien-4-ol (11).**[6] A flame-dried flask was cooled under a stream of nitrogen and charged with (4*R**,5*R**)-octa-1,7-diene-4,5-diol (1.5 g, 10.6 mmol). THF (10.6 mL) was added, the resulting solution was cooled to –78 °C, and *n*-BuLi (5.6 ml, 10.6 mmol, 1.9 M in hexanes) was added dropwise with stirring. The reaction mixture was allowed to warm to rt over 1 h and then a solution of TBSCl (1.59 g, 10.6 mmol) in THF (10.6 mL) was added slowly. The resulting mixture was stirred at rt for 30 min, then imidazole (36 mg, 0.53 mmol) was added and the mixture was stirred overnight at rt. A solution of saturated aqueous $NaHCO_3$ (5 mL) was added, and the resulting mixture was diluted with ethyl acetate (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 X 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel to afford the title compound as a pale yellow oil (1.8 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91–5.72 (m, 2 H), 5.13–5.04 (m, 4 H), 3.65–3.59 (m, 2 H), 2.49–2.39 (m, 1 H), 2.26–2.15 (m, 4 H), 0.9 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 134.1, 117.5, 116.9, 73.7, 71.7, 38.3, 25.7, 17.9, –4.2, –4.8; IR (film, cm^{-1}) 3450, 2930; MS(ESI): 279.1756 (279.1756 calcd for $C_{13}H_{28}SiO_2$, M + Na^+).

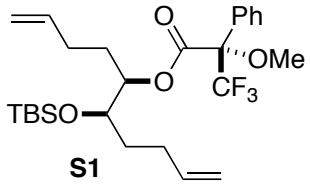


12

(±)-(5*R,6*R**)-6-(*tert*-Butyldimethylsiloxy)deca-1,9-dien-5-ol (12).** The conversion of (5*R**,6*R**)-deca-1,9-diene-5,6-diol (2.93 g, 17.24 mmol) to the title compound was achieved

using a procedure analogous to that described above for the preparation of **11**. This procedure afforded 2.65 g (54%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90–5.74 (m, 2 H), 5.07–4.94 (m, 4 H), 3.58–3.53 (m, 1 H), 3.51–3.45 (m, 1 H), 2.30–2.20 (m, 1 H), 2.18–2.00 (m, 4 H), 1.80–1.69 (m, 1 H), 1.59–1.45 (m, 3 H), 0.90 (s, 9 H), 0.04 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.3, 114.7, 114.6, 74.4, 71.8, 33.2, 32.8, 30.1, 29.2, 18.1, –4.2, –4.6; IR (film, cm^{-1}): 3459, 2953; MS(ESI): 307.2063 (307.2069 calcd for $C_{15}H_{32}SiO_2$, M + Na^+).

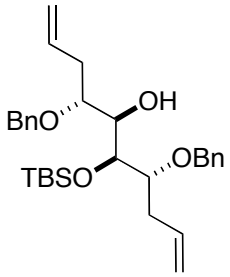
(–)-(5*R*,6*R*)-6-(*tert*-Butyldimethylsiloxy)deca-1,9-dien-5-ol (12). The conversion of (+)-(5*R*,6*R*)-deca-1,9-diene-5,6-diol[4] (1.19 g, 7.0 mmol) to the title compound was achieved using a procedure analogous to that described above for the preparation of **11**. This procedure afforded 1.29 g (44%) of the title compound as a pale yellow oil, $[\alpha]_D^{23}$ = –3.3° (*c* 0.42, CH_2Cl_2). The enantiopurity of this compound was judged to be 96% ee through ^{19}F NMR analysis of the corresponding Mosher ester derivative (**S1**).



S1

(–)-(2*S*,4*R*,5*R*)-5-[(*tert*-Butyldimethylsilyloxy)nona-1,8-dien-4-yl]-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S1). A flame-dried flask was cooled under a stream of nitrogen and charged with dimethylaminopyridine (4 mg, 0.035 mmol), DCC (40 mg, 0.193 mmol), (*S*)-α-methoxytrifluorophenylacetic acid (45 mg, 0.193 mmol) and THF (1 mL). A solution of (5*R*,6*R*)-6-(*tert*-butyldimethylsiloxy)deca-1,9-dien-5-ol (50 mg, 0.18 mmol) in THF (0.35 mL) was added dropwise, and the resulting mixture was stirred at rt until the starting material was consumed as judged by GC analysis. The reaction was diluted with cold pentane, filtered, and washed with brine. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 X 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel to afford the title compound as a clear oil (77 mg, 87%), $[\alpha]_D^{23}$ = –7.3° (*c* 0.70, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.46 (m, 2 H), 7.39–7.34 (m, 3 H), 5.79–5.66 (m, 1 H), 5.65–

5.53 (m, 1 H), 5.00–4.84 (m, 5 H), 3.70–3.64 (m, 1 H), 3.54–3.51 (s, 3 H), 2.14–1.90 (m, 3 H), 1.87–1.74 (m, 2 H), 1.70–1.59 (m, 1 H), 1.39–1.27 (m, 1 H), 1.26–1.16 (m, 1 H), 0.85 (s, 9 H), 0.10 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 138.0, 137.2, 132.1, 129.6, 128.4, 127.2, 119.4 (q, J = 186 Hz) 115.6, 114.8, 70.6, 55.7, 55.6, 34.9, 30.4, 30.1, 26.6, 25.8 (q, J = 49.6 Hz), 17.9, -4.4, –4.7 (one signal is missing due to incidental equivalence); ^{19}F NMR (376 MHz, $CDCl_3$) –71.4; IR (film, cm^{-1}) 2930, 1746, 1170; MS(ESI): 523.2457 (523.2467 calcd for $C_{26}H_{39}SiO_4F_3$, M + Na^+).



(–)-(**4*R*,5*R*,6*S*,7*R*)-4,7-Bis(benzyloxy)-6-(*tert*-butyldimethylsiloxy)deca-1,9-dien-5-ol (19).** The conversion of (4*R*,5*S*,6*S*,7*R*)-4,7-bis(benzyloxy)deca-1,9-diene-5,6-diol (1.76 g, 4.7 mmol) to the title compound was achieved using a procedure analogous to that described above for the preparation of **11**. This procedure afforded 0.9 g (50%) of the title compound as a colorless oil, $[\alpha]_D^{23} = -4.2^o$ (*c* 0.63, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 5 H), 7.27–7.24 (m, 4 H), 7.24–7.20 (m, 1 H), 5.99–5.87 (m, 1 H), 5.86–5.74 (m, 1 H), 5.19–4.95 (m, 4 H), 4.68 (d, J = 11.4 Hz, 1 H), 4.56 (d, J = 11.4 Hz, 1 H), 4.47 (d, J = 11.7 Hz, 1 H), 4.36 (d, J = 11.4 Hz, 1 H), 4.16 (t, J = 2.0 Hz, 1 H), 3.59–3.54 (m, 1 H), 3.48–3.40 (m, 2 H), 3.07 (d, J = 6.3 Hz, 1 H), 2.67–2.58 (m, 1 H), 2.54–2.45 (m, 1 H), 2.41–2.25 (m, 2 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 138.4, 135.4, 128.3, 128.2, 127.7, 127.6, 127.57, 125.5, 117.5, 117.0, 83.4, 78.9, 72.6, 71.4, 70.8, 70.4, 34.9, 33.6, 26.0, 18.3, –3.7, –4.9; IR (film, cm^{-1}) 3516, 3067; MS(ESI) 519.2907 (519.2921 calcd for $C_{30}H_{44}SiO_4$, M + Na^+).

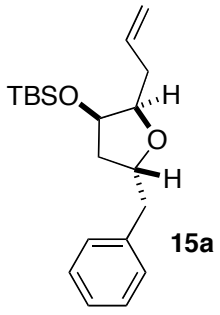
Synthesis of Bis-Tetrahydrofurans via Pd-Catalyzed Alkene Carboetherification

General Procedure 1: Palladium-Catalyzed Carboetherification Reactions for the Formation of Tetrahydrofuran Derivatives.[7] An oven or flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (2 mol% complex, 4 mol % Pd), Dpe-

phos (4 mol %), NaOtBu (2.0 equiv), and the aryl bromide (2.0 equiv). The tube was purged with nitrogen and the alcohol substrate (1.0 equiv), and THF or Toluene (0.25 M in substrate) were added. The mixture was heated to 65 °C or 110 °C with stirring until the starting material had been consumed as judged by GC or ^{1}H NMR analysis. The mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (2 mL), and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel.

General Procedure 2: Cleavage of TBS Protecting Groups.[8] An oven or flame-dried round-bottomed flask was cooled under a stream of nitrogen and charged with the protected alcohol (1.0 equiv). The tube was purged with nitrogen, THF (0.1 M in protected alcohol) was added, and the reaction was cooled to 0 °C. TBAF (10 equiv, 1 M in THF) was added dropwise and the reaction was warmed to rt. The mixture was stirred at rt until the starting material had been consumed as judged by GC analysis. The mixture was then quenched with 1 M HCl (5 mL) and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel.

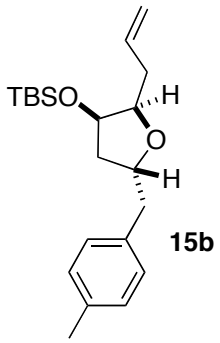
Synthesis of Fused-Ring Bis-Tetrahydrofurans (Table 1)



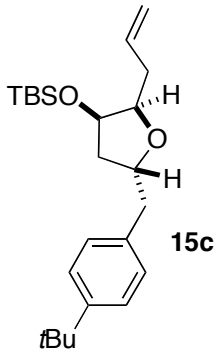
15a

(±)-(2*R,3*R**,5*R**)-(2-Allyl-5-benzyltetrahydrofuran-3-yloxy)(*tert*-butyl)dimethylsilane (15a, Table 1, Entries 1–2).** The coupling of (±)-**11** (400 mg, 1.56 mmol) with bromobenzene (330 μL, 3.13 mmol) was achieved following general procedure 1 using THF as solvent and a

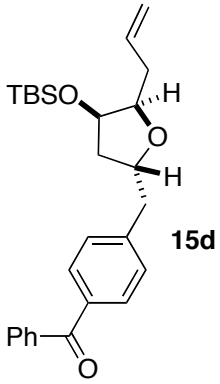
reaction temperature of 65 °C. This procedure afforded 385 mg (74%) of the title compound as an orange oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (m, 5 H), 5.95–5.83 (m, 1 H), 5.19–5.06 (m, 2 H), 4.55–4.46 (m, 1 H), 4.24–4.20 (m, 1 H), 3.90–3.85 (m, 1 H), 3.04–2.94 (dd, *J* = 5.5, 13.3 Hz, 1 H), 2.83–2.76 (dd, *J* = 7.1, 13.7 Hz, 1 H), 1.92–1.85 (m, 2 H), 1.79–1.71 (m, 1 H), 1.68–1.62, (m, 1 H), 0.91 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 135.7, 129.4, 128.2, 126.1, 116.3, 82.4, 73.3, 42.0, 41.0, 34.2, 25.7, 18.0, –4.5, –5.0; IR (film, cm^{-1}) 3030, 1472; MS(ESI): 355.2060 (355.2069 calcd for $C_{20}H_{32}SiO_2$, M + Na^+).



(±)-(2*R,3*R**,5*R**)-[2-Allyl-5-(4-methylbenzyl)tetrahydrofuran-3-yloxy](*tert*-butyl)dimethylsilane (15b, Table 1, Entries 3–4).** The coupling of (±)-**11** (200 mg, 0.78 mmol) with 4-bromotoluene (190 μL, 1.56 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 230 mg (85%) of the title compound as a red oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.07 (m, 4 H), 5.92–5.81 (m, 1 H), 5.17–5.03 (m, 2 H), 4.50–4.43 (m, 1 H), 4.21–4.17 (m, 1 H), 3.87–3.82 (m, 1 H), 2.94 (dd, *J* = 5.5, 8.1 Hz, 1 H), 2.74 (dd, *J* = 7.0, 13.7 Hz, 1 H), 2.76–2.69 (m, 2 H), 2.33 (s, 3 H), 1.89–1.82 (m, 1 H), 1.76–1.67 (m, 1 H), 0.88 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.5, 129.3, 128.9, 116.2, 82.3, 77.7, 73.3, 41.6, 41.0, 34.2, 25.7, 21.0, 18.0, –4.5, –5.1; IR (film, cm^{-1}) 2930, 1463. MS(ESI): 369.2213 (369.2226 calcd for $C_{21}H_{34}SiO_2$, M + Na^+).

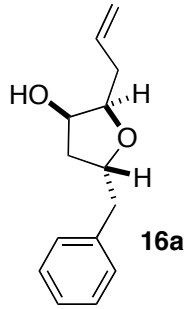


(±)-(2*R,3*R**,5*R**)-[2-Allyl-5-(4-*tert*-butylbenzyl)tetrahydrofuran-3-yloxy](*tert*-butyl)dimethylsilane (15c, Table 1, Entries 5–6).** The coupling of (±)-**11** (400 mg, 1.56 mmol) with 1-bromo-4-*tert*-butylbenzene (0.55 mL, 3.13 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 450 mg (74%) of the title compound as a red oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.2 Hz, 2 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 5.94–5.83 (m, 1 H), 5.18–5.05 (m, 2 H), 4.53–4.45 (m, 1 H), 4.22–4.19 (m, 1 H), 3.90–3.85 (m, 1 H), 2.93 (dd, *J* = 5.5, 16.0 Hz, 1 H), 2.75 (dd, *J* = 6.7, 12.0 Hz, 1 H), 2.45–2.29 (m, 2 H), 1.94–1.85 (m, 1 H), 1.80–1.71 (m, 1 H) 1.33 (s, 9 H), 0.89 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 140.4, 134.1, 130.1, 121.3, 87.3, 78.3, 46.6, 46.1, 39.4, 39.2, 36.4, 30.8, 23.1, 6.0, 0.5, 0.0; IR (film, cm^{-1}) 2957, 1471. MS(ESI): 411.2687 (411.2695 calcd for $C_{24}H_{40}SiO_2$, M + Na^+).



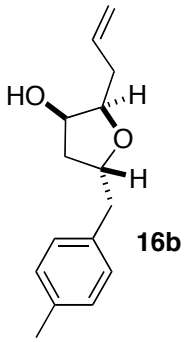
(±)-(2*R,4*R**,5*R**)-4-[5-Allyl-4-(*tert*-butyldimethylsilyloxy)tetrahydrofuran-2-ylmethyl]phenyl(phenyl)methanone (15d, Table 1, Entries 7–8).** The coupling of (±)-**11** (500 mg, 1.95 mmol) with 4-bromobenzophenone (1.02 g, 3.9 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded

300 mg (42%) of the title compound as an amber oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.15 (m, 9 H); 5.91–5.79 (m, 1 H), 5.15–5.03 (m, 2 H), 4.56–4.46 (m, 1 H), 4.23–4.19 (m, 1 H), 3.87–3.22 (m, 1 H), 2.99 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.88 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.44–2.27 (m, 1 H), 1.89 (dd, *J* = 1.6, 5.9 Hz, 1 H), 1.85 (dd, *J* = 5.9, 7.0 Hz, 1 H), 1.77–1.69 (m, 1 H), 0.88 (s, 9 H), 0.05 (s, 3 H), (0.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 143.7, 137.8, 135.6, 132.2, 130.2, 129.9, 129.4, 128.2, 116.4, 82.5, 73.2, 42.0, 41.3, 34.1, 25.7, 18.0, –4.5, –5.0 (one carbon signal is absent due to incidental equivalence); IR (film, cm^{-1}) 2928, 1700, 1278. MS(ESI): 459.2330 (459.2331 calcd for $C_{27}H_{36}SiO_3$, M + Na^+).

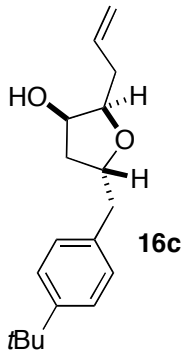


16a

(±)-(2*R,3*R**,5*R**)-2-Allyl-5-benzyltetrahydrofuran-3-ol (16a, Table 1, Entries 1–2)**. Removal of the TBS protecting group from **15a** (198 mg, 0.593 mmol) with TBAF (5.93 mL, 5.93 mmol) was achieved following general procedure 2. This procedure afforded 127 mg (97%) of the title compound as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.19 (m, 5 H), 5.92–5.81 (m, 1 H), 5.21–5.07 (m, 2 H), 4.54–4.45 (m, 1 H), 4.25–4.20 (m, 1 H), 3.87 (dt, *J* = 2.7, 7.0 Hz, 1 H), 2.97 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.78–2.63 (m, 1 H), 2.51–2.35 (m, 2 H), 1.98 (dd, *J* = 6.3, 13.3 Hz, 1 H), 1.85–1.77 (m, 1 H), 1.68 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 134.8, 129.4, 128.3, 126.3, 117.0, 81.4, 77.8, 73.1, 42.0, 40.8, 33.8; IR (film, cm^{-1}) 3411, 2925, 1454. MS(ESI): 241.1201 (241.1204 calcd for $C_{14}H_{18}O_2$, M + Na^+).

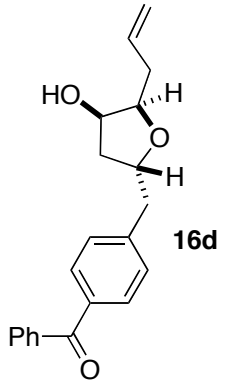


(±)-(2*R,3*R**,5*R**)-2-Allyl-5-(4-methylbenzyl)tetrahydrofuran-3-ol (16b, Table 1, Entries 3–4).** Removal of the TBS protecting group from **15b** (181 mg, 0.52 mmol) with TBAF (5.2 mL, 5.2 mmol) was achieved following general procedure 2. This procedure afforded 113 mg (93%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 4 H), 5.92–5.81 (m, 1 H), 5.21–5.06 (m, 2 H), 4.51–4.43 (m, 1 H), 4.26–4.20 (m, 1 H), 3.86 (dt, *J* = 2.7, 7.1 Hz, 1 H), 2.93 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.71 (dd, *J* = 7.0, 13.7 Hz, 1 H), 2.51–2.34 (m, 2 H), 2.31 (s, 3 H), 2.01–1.95 (m, 1 H), 1.85–1.77 (m, 1 H), 1.61–1.53 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.0, 134.9, 129.3, 129.0, 117.0, 81.5, 77.9, 72.9, 41.6, 40.7, 33.8, 21.0; IR (film, cm^{-1}) 3451, 2985, 1422. MS(ESI): 255.1352 (255.1361 calcd for $C_{15}H_{20}O_2$, M + Na^+).

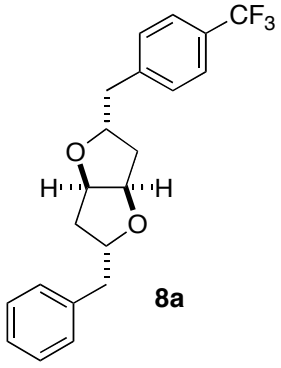


(±)-(2*R,3*R**,5*R**)-2-Allyl-5-(4-*tert*-butylbenzyl)tetrahydrofuran-3-ol (16c, Table 1, Entries 5–6).** Removal of the TBS protecting group from **16b** (100 mg, 0.287 mmol) with TBAF (2.87 mL, 2.87 mmol) was achieved following general procedure 2. This procedure afforded 65 mg (92%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.32 (m, 2 H), 7.17–7.12 (m, 2 H), 5.93–5.82 (m, 1 H), 5.22–5.07 (m, 2 H), 4.53–4.44 (m, 1 H), 4.24 (t, *J* = 3.5 Hz, 1 H), 3.90 (dt, *J* = 6.7, 7.0 Hz, 1 H), 2.95 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.71 (dd, *J* = 7.0, 13.7 Hz, 1 H), 2.39–2.06 (m, 2 H), 2.05–1.97 (m, 1 H), 1.87–1.78, (m, 1 H), 1.67 (s, 1 H), 1.31 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 135.1, 134.9, 129.0, 125.2, 117.0, 81.5, 77.9, 72.9,

41.6, 41.0, 34.4, 33.8, 31.4; IR (film, cm^{-1}) 3418, 2963, 1363. MS(ESI): 297.1826 (297.1830 calcd for $C_{18}H_{26}O_2$, M + Na^+).

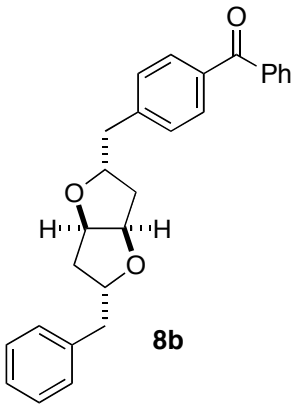


(±)-(2*R,4*R**,5*R**)-4-(5-Allyl-4-hydroxytetrahydrofuran-2-ylmethyl)phenyl(phenyl)methanone (16d, Table 1, Entries 7–8).** Removal of the TBS protecting group from **15d** (30 mg, 0.077 mmol) with TBAF (77 μL, 0.77 mmol) was achieved following general procedure 2. This procedure afforded 23 mg (92%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.71 (m, 4 H), 7.60–7.54 (m, 1 H), 7.49–7.43 (m, 2 H), 7.35–7.30 (m, 2 H), 5.91–5.79 (m, 1 H), 5.19–5.05 (m, 2 H), 4.57–4.48 (m, 1 H), 4.24 (s, 1 H), 3.87 (dt, *J* = 2.7, 7.0 Hz, 1 H), 2.99 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.85 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.50–2.34 (m, 2 H), 2.02 (dd, *J* = 6.3, 13.7 Hz, 2 H), 1.85–1.77 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6; 143.5, 137.7, 135.6, 134.8, 132.3, 130.3, 130.0, 129.4, 128.2, 117.1, 81.6, 72.9, 42.0, 40.9, 33.8 (one carbon signal is absent due to incidental equivalence; IR (film, cm^{-1}) 3474, 2932, 1265. MS(ESI): 345.1468 (345.1467 calcd for $C_{21}H_{22}O_3$, M + Na^+).



(±)-(2*R,3a*R**,5*R**,6a*R**)-2-Benzyl-5-[4-(trifluoromethyl)benzyl]hexahydrofuro[3,2-b]furan (8a, Table 1, Entry 1).** The coupling of **16a** (31 mg, 0.14 mmol) with 4-bromobenzotrifluoride

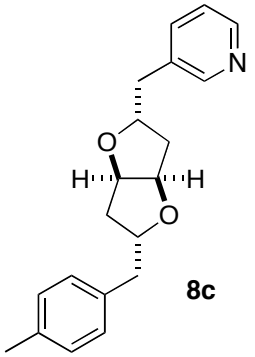
(60 μL, 0.28 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 45 mg (87%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.34 (d, *J* = 7.8 Hz, 2 H), 7.17–7.08 (m, 4 H), 7.06–7.01 (m, 3 H), 4.55–4.50 (m, 2 H), 4.14–4.05 (m, 2 H), 2.77–2.70 (m, 2 H), 2.66 (dd, *J* = 5.5, 13.7 Hz, 1 H), 2.57 (dd, *J* = 6.3, 13.7 Hz, 1 H), 1.94 (dt, *J* = 1.5, 12.5 Hz, 2 H), 1.54–1.40 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 138.2, 129.3 (q, *J* = 183 Hz, 1 C), 128.3, 128.2, 125.2 (q, *J* = 60 Hz), 83.8, 83.7, 83.68, 83.52, 77.3, 41.7, 41.4, 40.7, 40.66 (one signal is absent due to incidental equivalence); IR (film, cm^{-1}) 2936, 1325, 1113. MS(ESI): 385.1406 (385.1391 calcd for $C_{21}H_{21}F_3O_2$, M + Na^+).



8b

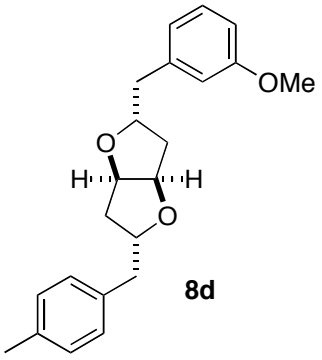
(±)-(2*R,3a*R**,5*R**,6a*R**)-4-(5-Benzylhexahydrofuro[3,2-b]furan-2-ylmethyl)phenyl(phenyl)methanone (8b, Table 1, Entry 2).** The coupling of **16a** (31 mg, 0.14 mmol) with 4-bromobenzophenone (74 mg, 0.28 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 55 mg (96%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.60 (m, 2 H), 7.59–7.55 (m, 2 H), 7.44–7.38 (m, 1 H), 7.34–7.28 (m, 2 H), 7.19–7.01 (m, 7 H), 4.56–4.51 (m, 2 H), 4.17–4.06 (m, 2 H), 2.81–2.71 (m, 2 H), 2.67 (dd, *J* = 5.9, 7.8 Hz, 1 H), 2.57 (dd, *J* = 6.7, 13.7 Hz, 1 H), 2.01–1.90 (m, 2 H), 1.55–1.46 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 143.4, 138.1, 137.7, 135.6, 132.2, 130.2, 130.0, 129.2, 129.1, 128.3, 128.2,

126.2, 83.7, 83.5, 80.6, 80.0, 41.7, 41.6, 40.7, 40.6; IR (film, cm^{-1}) 2993, 1759, 1246. MS(ESI): 421.1771 (421.1780 calcd for $C_{27}H_{26}O_3$, M + Na^+).



8c

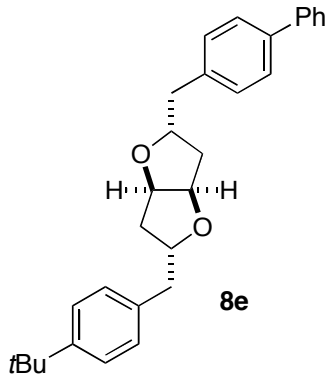
(±)-(2*R,3a*R**,5*R**,6a*R**)-3-[5-(4-Methylbenzyl)hexahydrofuro[3,2-b]furan-2-ylmethyl]pyridine (8c, Table 1, Entry 3).** The coupling of **16b** (56 mg, 0.24 mmol) with 3-bromopyridine (47 μL, 0.48 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 75 mg (92%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47–8.40 (m, 2 H), 7.55–7.51 (m, 1 H), 7.22–7.17 (m, 1 H), 7.08 (s, 4 H), 4.69–4.64 (m, 2 H), 4.28–4.18 (m, 2 H), 2.89–2.74 (m, 3 H), 2.68 (dd, *J* = 6.4, 7.0 Hz, 1 H), 2.30 (s, 3 H), 2.14–2.03 (m, 2 H), 1.69–1.58 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 147.7, 136.7, 137.7, 135.6, 134.9, 129.0, 128.9, 123.1, 83.7, 83.4, 80.7, 79.6, 41.2, 40.52, 40.5, 38.5, 20.9; IR (film, cm^{-1}) 3053, 1265. MS(ESI): 310.1810 (310.1807 calcd for $C_{20}H_{23}O_2N$, M + H^+).



8d

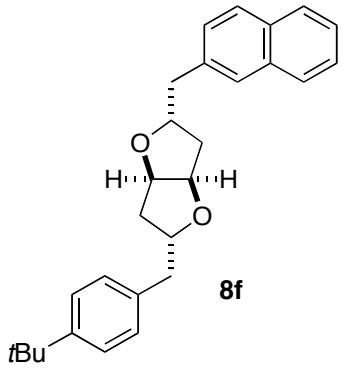
(±)-(2*R,3a*R**,5*R**,6a*R**)-2-(3-Methoxybenzyl)-5-(4-methylbenzyl)hexahydrofuro[3,2-b]furan (8d, Table 1, Entry 4).** The coupling of **16b** (40 mg, 0.34 mmol) with 3-bromoanisole

(43 μL, 0.34 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 48 mg (82%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.18 (m, 1 H), 7.10 (s, 4 H), 6.82–6.75 (m, 3 H), 4.72–4.68 (m, 2 H), 4.32–4.22 (m, 2 H), 3.80 (s, 3 H), 2.94–2.85 (m, 2 H), 2.74–2.67 (m, 2 H), 2.33 (s, 3 H), 2.13 (q, *J* = 2.4 Hz, 1 H), 2.09 (q, *J* = 2.3 Hz, 1 H), 1.71–1.62 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 139.9, 135.7, 135.1, 129.3, 129.1, 129.0, 121.7, 115.1, 111.5, 83.7, 83.6, 80.7, 80.4, 55.1, 41.8, 41.3, 40.8, 40.7, 21.0; IR (film, cm^{-1}) 2920, 1259. MS(ESI): 361.1788 (361.1780 calcd for $C_{22}H_{26}O_3$, M + Na^+).



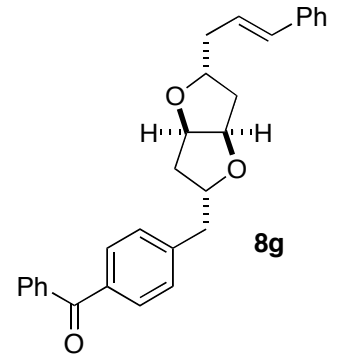
8e

(±)-(2*R,3a*R**,5*R**,6a*R**)-2-(Biphenyl-4-ylmethyl)-5-(4-*tert*-butylbenzyl)hexahydrofuro[3,2-b]furan (8e, Table 1, Entry 5).** The coupling of **16c** (46 mg, 0.2 mmol) with 4-bromobiphenyl (46 mg, 0.2 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 35 mg (83%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2 H), 7.56–7.52, (m, 2 H), 7.49–7.43 (m, 2 H), 7.38–7.28 (m, 5 H), 7.16 (d, *J* = 8.2 Hz, 2 H), 4.75 (d, *J* = 4.9 Hz, 2 H), 4.37–4.26 (m, 2 H), 2.94 (dt, *J* = 6.3, 14.0 Hz, 2 H), 2.81 (dd, *J* = 6.3, 13.9 Hz, 1 H), 2.72 (dd, *J* = 6.4, 13.7 Hz, 1 H), 2.20–2.12 (m, 2 H), 1.77–1.64 (m, 2 H), 1.34 (s, 9 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 141.0, 139.2, 137.4, 135.2, 129.7, 129.0, 128.7, 127.1, 127.0, 125.2, 83.7, 83.6, 80.7, 80.5, 41.4, 41.3, 40.9, 40.8, 34.4, 31.4 (one carbon signal is missing due to incidental equivalence); IR (film, cm^{-1}) 2900, 1091. MS(ESI): 427.2628 (427.2637 calcd for $C_{30}H_{34}O_2$, M + H^+).



8f

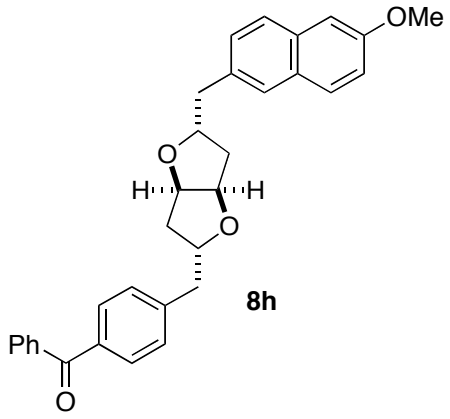
(±)-(2*R,3a*R**,5*R**,6a*R**)-2-(4-*tert*-Butylbenzyl)-5-(naphthalen-2-ylmethyl)hexahydrofuro[3,2-b]furan (8f, Table 1, Entry 6).** The coupling of **16c** (41 mg, 0.2 mmol) with 2-bromonapthalene (41 mg, 0.2 mmol) was achieved following the general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 36 mg (90%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.76 (m, 3 H), 7.66 (s, 1 H), 7.50–7.41 (m, 2 H), 7.38–7.34 (m, 1 H), 7.33–7.29 (m, 2 H), 7.17–7.12 (m, 2 H), 4.74–4.71 (m, 2 H), 4.43–4.34 (m, 1 H), 4.33–4.24 (m, 1 H), 3.07 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.96–2.87 (m, 2 H), 2.17–2.09 (m, 2 H), 1.77–1.64 (m, 3 H), 1.32 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 135.9, 135.2, 133.5, 132.2, 128.8, 127.9, 127.8, 127.6, 127.6, 127.5, 125.9, 125.3, 125.2, 83.7, 83.6, 80.7, 80.5, 41.8, 41.3, 40.9, 40.8, 34.4, 31.4 (two carbon signals are missing due to incidental equivalence; IR (film, cm^{-1}) 2960, 1091. MS(ESI): 423.2292 (423.2300 calcd for $C_{28}H_{32}O_2$, M + Na^+).



8g

(±)-4-(2*R,3a*R**,5*R**,6a*R**)-4-(5-Cinnamylhexahydrofuro[3,2-b]furan-2-ylmethyl)phenyl(phenyl)methanone (8g, Table 1, Entry 7).** The coupling of **16d** (70 mg, 0.23 mmol) with β-bromostyrene (58 μL, 0.45 mmol) was achieved following general procedure 1

using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 68 mg (70%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis^{1}H NMR (400 MHz, $CDCl_3$) 7.79–7.21 (m, 3 H), 7.59–7.54 (m, 1 H), 7.49–7.43 (m, 2 H), 7.34–7.30 (m, 4 H), 7.29–7.24 (m, 2 H), 7.24–7.16 (m, 2 H), 6.43 (d, *J* = 16.0 Hz, 1 H), 6.22–6.13 (m, 1 H), 4.74–4.69 (m, 2 H), 4.36–4.29 (m, 1 H), 4.19–4.12 (m, 1 H), 2.95 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.85 (dd, *J* = 5.9, 7.8 Hz, 1 H), 2.51–2.35 (m, 2 H), 2.20–2.11 (m, 2 H), 1.73–1.64 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 143.4, 137.7, 137.3, 135.6, 132.2, 132.1, 130.2, 130.0, 129.1, 128.4, 128.1, 127.0, 126.0, 83.8, 83.5, 80.0, 79.5, 41.6, 40.7, 40.5, 38.8 (one signal is absent due to incidental equivalence); IR (film, cm^{-1}) 2920, 1700, 1278. MS(ESI): 447.1938 (447.193 calcd for $C_{29}H_{28}O_3$, M + Na^+).

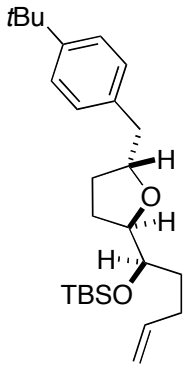


8h

(±)-(2*R,3a*R**,5*R**,6a*R**)-4-[5-(6-Methoxynaphthalen-2-ylmethyl)hexahydrofuro[3,2-b]furan-2-ylmethyl]phenyl(phenyl)methanone (8h, Table 1, Entry 8).** The coupling of **16d** (50 mg, 0.16 mmol) with 2-bromo-6-methoxynaphthalene (70 mg, 0.32 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 70 mg (91%) of the title compound as an orange oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.77 (m, 3 H), 7.75–7.71 (m, 3 H), 7.67 (q, *J* = 5.5 Hz, 2 H), 7.50–7.44 (m, 2 H), 7.31 (d, *J* = 8.2 Hz, 3 H), 7.14–7.09 (m, 2 H), 4.73–4.68 (m, 2 H), 4.39–4.27 (m, 2 H), 3.90 (s, 3 H), 3.03 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.98–2.81 (m, 3 H), 2.17–2.08 (m, 2 H), 1.76–1.63 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 157.2, 143.4, 137.7, 135.6, 133.3, 133.1, 132.1, 130.2, 129.9, 129.1, 129.0, 128.2, 128.1, 127.3, 126.6, 118.6, 105.4, 83.7, 83.5, 80.7, 79.9, 55.2,

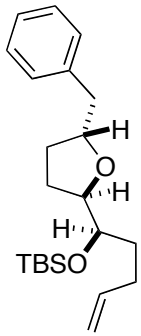
41.6, 40.7, 40.6 (two carbons signals are absent due to incidental equivalence); IR (film, cm^{-1}) 2935, 1657, 1278. MS(ESI): 501.2053 (501.2042 calcd for $C_{32}H_{30}O_4$, M + Na^+).

Synthesis of Attached-Ring Bis-Tetrahydrofurans (Table 2)



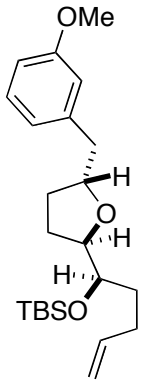
17a

(±)-(1*R,2*R**,5*R**)-*tert*-Butyl 1-[5-(4-*tert*-butylbenzyl)tetrahydrofuran-2-yl]pent-4-enyloxy)dimethylsilane (17a, Table 2, Entries 1–2)**. The coupling of (±)-**12** (400 mg, 1.4 mmol) with 1-bromo-4-*tert*-butylbenzene (0.5 mL, 2.8 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 460 mg (79%) of the title compound as an amber oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2 H), 7.17–7.13 (m, 2 H), 5.88–5.76 (m, 1 H), 5.05–4.92 (m, 2 H), 4.17–4.09 (m, 1 H), 3.96 (dd, *J* = 6.3, 18.0 Hz, 1 H), 3.63–3.57 (m, 1 H), 2.91 (dd, *J* = 6.1, 13.7 Hz, 1 H), 2.69 (dd, *J* = 7.0, 13.5 Hz, 1 H), 2.26–2.15 (m, 1 H), 2.13–2.02 (m, 1 H), 1.95–1.84 (m, 2 H), 1.70–1.49 (m, 3 H) 1.46–1.39 (m, 1 H), 1.31 (s, 9 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 139.0, 129.0, 125.1, 114.3, 81.5, 80.1, 74.4, 41.4, 34.3, 32.0, 31.9, 31.4, 30.0, 27.4, 26.0, 25.9, –4.2, –4.7; IR (film, cm^{-1}) 2930, 1089. MS(ESI): 439.3005 (439.3008 calcd for $C_{26}H_{44}SiO_2$, M + Na^+).



17b

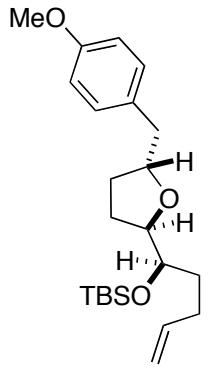
(±)-(1*R,2*R**,5*R**)-1-[(5-Benzyltetrahydrofuran-2-yl)pent-4-enyloxy](*tert*-butyl)dimethylsilane (17b, Table 2, Entries 3–4),** The coupling of (±)-**12** (400 mg, 1.4 mmol) with bromobenzene (0.3 mL, 2.8 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 350 mg (68%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.15 (m, 5 H), 5.86–5.75 (m, 1 H), 5.03–4.90 (m, 2 H), 3.94 (q, *J* = 13.9 Hz, 1 H), 3.61–3.55 (m, 1 H), 2.92 (dd, *J* = 5.9, 13.5 Hz, 1 H), 2.69 (dd, *J* = 7.0, 13.5 Hz, 1 H), 2.24–2.13 (m, 1 H), 2.11–2.00 (m, 1 H), 1.91–1.77 (m, 2 H), 1.68–1.48 (m, 4 H), 1.46–1.36 (m, 1 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 138.8, 129.2, 128.1, 126.0, 114.3, 81.5, 80.0, 74.4, 41.9, 32.1, 31.7, 29.9, 27.4, 26.0, –4.2, –4.7; IR (film, cm^{-1}) 2930, 1078. MS(ESI): 383.2373 (383.2382 calcd for $C_{22}H_{36}SiO_2$, M + Na^+).



17c

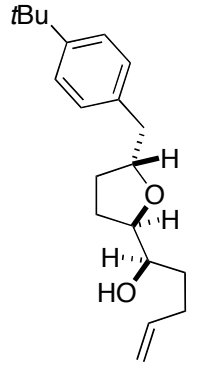
(±)-(1*R,2*R**,5*R**)-*tert*-Butyl 1-{[5-(3-methoxybenzyl)tetrahydrofuran-2-yl]pent-4-enyloxy}dimethylsilane (17c, Table 2, Entries 5–6).** The coupling of (±)-**12** (400 mg, 1.4 mmol) with 3-bromoanisole (0.36 mL, 2.8 mmol) was achieved following the general procedure 1 using THF solvent and a reaction temperature of 65 °C. This procedure afforded 360 mg (65%)

of the title compound as an orange oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.8 Hz, 1 H), 6.82–6.73 (m, 3 H), 5.88–5.76 (m, 1 H), 5.05–4.92 (m, 2 H), 4.19–4.11 (m, 1 H), 3.96 (q, *J* = 6.2 Hz, 1 H), 3.79 (s, 3 H), 3.63–3.57 (m, 1 H), 2.81 (dd, *J* = 5.9, 13.5 Hz, 1 H), 2.70 (dd, *J* = 7.0, 13.5 Hz, 1 H), 2.25–2.14 (m, 1 H), 1.94–1.83 (m, 2 H) 1.71–1.49 (m, 4 H), 1.49–1.37 (m, 1 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 140.4, 139.0, 129.1, 121.8, 115.0, 114.4, 111.5, 81.6, 80.0, 74.4, 55.1, 42.0, 32.1, 31.8, 30.0, 27.4, 26.0, –4.2, –4.7; IR (film, cm^{-1}) 2928, 1062. MS(ESI): 413.2482 (413.2488 calcd for $C_{23}H_{38}SiO_3$, M + Na^+).



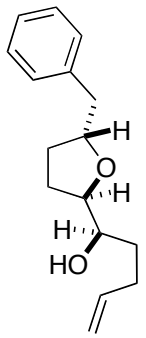
17d

(±)-(1*R,2*R**,5*R**)-1-{[5-(4-Methoxybenzyl)tetrahydrofuran-2-yl]pent-4-enyloxy}dimethylsilane (17d, Table 2, Entries 7–8).** The coupling of (±)-**12** (400 mg, 1.4 mmol) with 4-bromoanisole (0.36 mL, 2.8 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 310 mg (56%) of the title compound as an orange oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.10 (m, 2 H), 6.84–6.79 (m, 2 H), 5.88–5.75 (m, 1 H), 5.05–4.89 (m, 2 H), 4.14–4.05 (m, 1 H), 3.98–3.90 (m, 1 H), 3.78 (d, *J* = 4.1 Hz, 1 H), 3.58 (s, 3 H), 3.48–3.39 (m, 1 H), 2.91–2.84 (m, 1 H), 2.69–2.61 (m, 1 H), 2.12–2.00 (m, 1 H), 1.92–1.81 (m, 2 H), 1.70–1.49 (m, 3 H), 1.49–1.33 (m, 1 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 138.9, 130.8, 130.2, 114.3, 113.6, 81.4, 80.1, 74.3, 55.1, 40.9, 32.0, 31.6, 30.0, 27.3, 25.9, –4.2, –4.8; IR (film, cm^{-1}) 2929, 1040. MS(ESI): 413.2474 (413.2488 calcd for $C_{23}H_{38}SiO_3$, M + Na^+).



18a

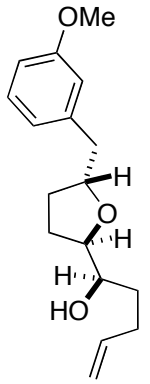
(±)-(1*R,2*R**,5*R**)-1-[5-(4-*tert*-Butylbenzyl)tetrahydrofuran-2-yl]pent-4-en-1-ol (18a, Table 2, Entries 1–2).** Removal of the TBS protecting group from **17a** (26 mg, 0.067 mmol) with TBAF (0.67 mL, 0.67 mmol) was achieved following general procedure 2. This procedure afforded 18 mg (96%) of the title compound as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2 H), 7.17–7.13, (m, 2 H), 5.90–5.73 (m, 1 H), 5.09–4.94 (m, 2 H), 4.19–4.10 (m, 1 H), 3.89–3.82 (q, *J* = 7.0 Hz, 1 H), 3.44–3.36 (m, 1 H), 2.93 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.69, (dd, *J* = 8.0, 13.7 Hz, 1 H), 2.40–2.34 (d, *J* = 3.7 Hz, 1 H), 2.31–2.20 (m, 1 H), 2.18–2.06 (m, 1 H), 1.99–1.87 (m, 2 H), 1.65–1.40 (m, 4 H), 1.27 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 138.5, 135.5, 128.9, 114.7, 82.1, 80.0, 77.3, 73.4, 41.3, 34.3, 32.5, 32.0, 31.3, 29.8, 28.2; IR (film, cm^{-1}) 3436, 2964, 1060. MS(ESI): 325.2141 (325.2144 calcd for $C_{20}H_{30}O_2$, M + Na^+).



18b

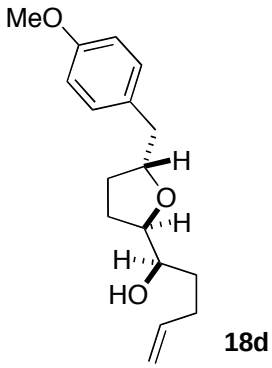
(±)-(1*R,2*R**,5*R**)-1-(5-Benzyltetrahydrofuran-2-yl)pent-4-en-1-ol (18b, Table 2, Entries 3–4).** Removal of the TBS protecting group from **18a** (36 mg, 0.1 mmol) with TBAF (1.0 mL, 1.0 mmol) was achieved following general procedure 2. This procedure afforded 22 mg (92%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 3 H), 7.29–7.24 (m, 2 H), 5.95–5.83 (m, 1 H), 5.14–5.00 (m, 2 H), 4.25–4.17 (m, 1 H), 3.90 (q, *J* = 7.0 Hz, 1 H), 3.49–3.43 (m, 1 H), 3.01 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.78 (dd, *J* = 7.0, 13.7 Hz 1 H), 2.45 (s, 1 H), 2.40–2.30 (m, 1 H), 2.27–2.16 (m, 1 H), 2.07–1.95 (m, 2 H), 1.74–1.62 (m, 2 H), 1.59–1.51

(m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.5, 129.3, 128.3, 126.2, 114.7, 82.2, 79.9, 73.4, 41.8, 32.5, 31.9, 29.8, 28.2; IR (film, cm^{-1}) 3449, 2964, 1073. MS(ESI): 269.1514 (269.1517 calcd for $C_{16}H_{22}O_2$, M + Na^+).



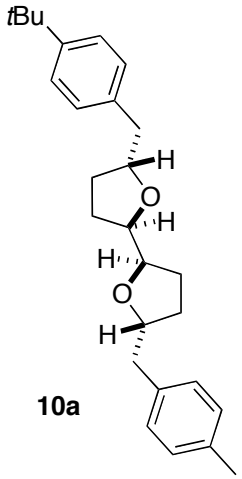
18c

(±)-(1*R,2*R**,5*R**)-1-[5-(3-Methoxybenzyl)tetrahydrofuran-2-yl]pent-4-en-1-ol (18c, Table 2, Entries 5–6).** Removal of the TBS protecting group from **17c** (250 mg, 0.64 mmol) with TBAF (6.4 mL, 6.4 mmol) was achieved following general procedure 2. This procedure afforded 170 mg (97%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.17 (m, 2 H), 6.82–6.74 (m, 2 H), 5.89–5.77 (m, 1 H), 5.08–4.94 (m, 2 H), 4.19–4.10 (m, 1 H), 3.87–3.80 (m, 1 H), 3.79 (s, 3 H), 3.43–3.38 (m, 1 H), 2.93 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.70 (dd, *J* = 6.7, 13.7 Hz, 1 H), 2.35–2.24 (m, 1 H), 2.21–2.10 (m, 1 H), 2.02–1.90 (m, 2 H), 1.68–1.57 (m, 2 H), 1.54–1.45 (m, 2 H) (the OH proton signal was not detected due to broadening); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 140.2, 138.5, 129.2, 121.7, 115.0, 114.7, 111.5, 82.2, 79.9, 73.4, 55.1, 41.9, 32.6, 32.0, 30.0, 28.2; IR (film, cm^{-1}) 3453, 2937, 1046. MS(ESI): 299.1617 (299.1623 calcd for $C_{17}H_{24}O_3$, M + Na^+).



18d

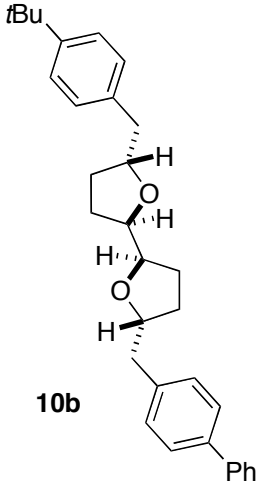
(±)-(1*R,2*R**,5*R**)-1-[5-(4-Methoxybenzyl)tetrahydrofuran-2-yl]pent-4-en-1-ol (18d, Table 2, Entries 7–8).** Removal of the TBS protecting group from **17d** (290 mg, 0.74 mmol) with TBAF (7.4 mL, 7.4 mmol) was achieved following general procedure 2. This procedure afforded 190 mg (94%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.11 (m, 2 H), 6.85–6.81 (m, 2 H), 5.89–5.77 (m, 1 H), 5.08–4.94 (m, 2 H), 4.15–4.07 (m, 1 H), 3.86–3.80 (m, 1 H), 3,79 (s, 3 H), 3.43–3.36 (m, 1 H), 2.88 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.67 (dd, *J* = 6.7, 13.7 Hz, 1 H), 2.37 (s, 1 H), 2.36–2.24 (m, 1 H), 2.21–2.12 (m, 1 H), 2.00–1.89 (m, 2 H), 1.66–1.56 (m, 2 H), 1.54–1.46 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 138.4, 130.6, 130.2, 114.7, 113.7, 82.1, 80.1, 73.4, 55.1, 40.8, 32.5, 31.7, 29.8, 28.2; IR (film, cm^{-1}) 3469, 2918, 1036. MS(ESI): 299.1622 (299.1623 calcd for $C_{17}H_{24}O_3$, M + Na^+).



10a

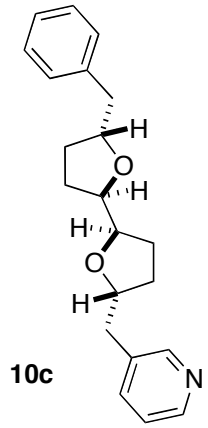
(±)-(2*R,2'*R**,5*R**,5'*R**)-5-(4-*tert*-Butylbenzyl)-5'-(4-methylbenzyl)octahydro-2,2'-bifuran (10a, Table 2, Entry 1).** The coupling of **18a** (30 mg, 0.11 mmol) with 4-bromotoluene (28 μL, 0.22 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 30 mg (67%) of the title compound as an amber

oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.20 (m, 2 H), 7.19 (s, 1 H), 7.08–7.04 (m, 2 H), 7.01 (s, 3 H), 4.16–4.08 (m, 2 H), 3.90–3.84 (m, 2 H), 3.02–2.95 (m, 2 H), 2.56 (dd, *J* = 8.2, 13.3 Hz, 2 H), 2.24 (s, 3 H), 1.90–1.78 (m, 4 H), 1.56–1.44 (m, 4 H), 1.23 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 135.7, 135.6, 135.5, 129.2, 129.0, 128.9, 125.1, 81.7, 81.6, 80.5, 80.4, 41.5, 41.5, 34.3, 31.6, 31.4, 31.39, 29.8, 28.3, 21.0; IR (film, cm^{-1}) 2900, 1051. MS(ESI): 415.2594 (415.2613 calcd for $C_{27}H_{36}O_2$, M + Na^+).



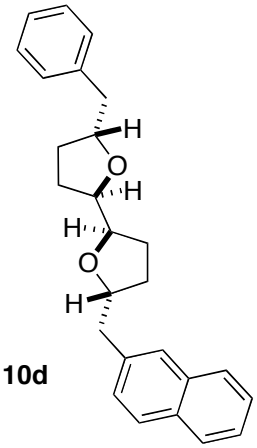
10b

(±)-(2*R,2'*R**,5*R**,5'*R**)-5-(Biphenyl-4-ylmethyl)-5'-(4-*tert*-butylbenzyl)octahydro-2,2'-bifuran** (**10b, Table 2, Entry 2**). The coupling of **18a** (50 mg, 0.17 mmol) with 4-bromobiphenyl (80 mg, 0.34 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 46 mg (61%) of the title compound as a yellow oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2 H), 7.55–7.50 (m, 2 H), 7.44 (t, *J* = 7.4 Hz, 2 H), 7.37–7.28, (m, 5 H), 7.15 (d, *J* = 8.2 Hz, 2 H), 4.31–4.17 (m, 2 H), 4.02–3.94 (m, 2 H), 3.11 (dt, *J* = 5.1, 13.9 Hz, 2 H), 2.75 (dd, *J* = 8.0, 13.5 Hz, 1 H), 2.65 (dd, *J* = 8.4, 13.3 Hz, 1 H), 2.00–1.89 (m, 4 H), 1.69–1.55 (m, 4 H), 1.32 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 141.0, 139.0, 137.9, 135.6, 129.7, 128.9, 128.7, 127.0, 126.9, 125.1, 81.7, 81.6, 80.5, 80.3, 41.6, 41.4, 34.3, 31.5, 29.8, 28.3 (three carbon signals are absent due to incidental equivalence); IR (film, cm^{-1}) 2910, 1049. MS(ESI): 477.2776 (477.2770 calcd for $C_{32}H_{38}O_2$, M + Na^+).



10c

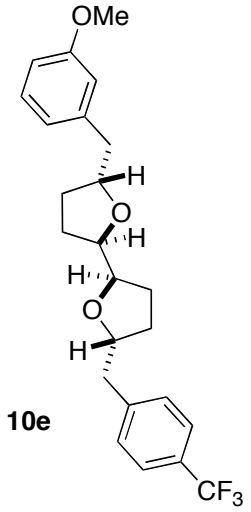
(±)-(2*R,2'*R**,5*R**,5'*R**)-3-[5'-Benzyloctahydro-2,2'-bifuran-5-yl)methyl]pyridine (10c, Table 2, Entry 3).** The coupling of **18b** (25 mg, 0.1 mmol) with 3-bromopyridine (20 μL, 0.2 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 20 mg (61%) of the title compound as an amber oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 2 H), 7.55 (d, *J* = 7.6, 1 H), 7.26–7.13 (m, 6 H), 4.19–4.08 (m, 2 H), 3.92–3.84 (m, 2 H), 3.01 (dd, *J* = 5.1, 13.0 Hz, 2 H), 2.93 (dd, *J* = 5.7, 13.9 Hz, 2 H), 1.94–1.81 (m, 4 H), 1.64–1.44 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 147.6, 138.7, 136.9, 134.2, 129.3, 128.2, 126.1, 123.2, 81.8, 81.5, 80.5, 79.6, 41.9, 38.9, 31.4, 31.3, 29.7, 28.3; IR (film, cm^{-1}) 2917, 1068. MS(ESI): 324.1960 (324.1964 calcd for $C_{21}H_{25}O_2N$, M + H^+).



10d

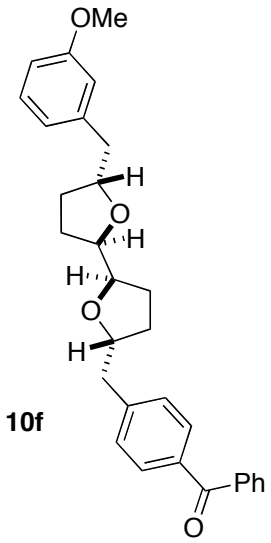
(±)-(2*R,2'*R**,5*R**,5'*R**)-5-Benzyl-5'-(naphthalen-2-ylmethyl)octahydro-2,2'-bifuran (10d, Table 2, Entry 4).** The coupling of **18b** (50 mg, 0.17 mmol) with 2-bromonaphthalene (36 mg, 0.34 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 40 mg (65%) of the title compound as an orange

oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, CD_3CF_2OD) δ 8.48–8.39 (m, 3 H), 8.33–8.27 (m, 1 H), 8.15–8.04 (m, 2 H), 8.04–7.82 (m, 6 H), 5.01–4.83 (m, 2 H), 4.69–4.60 (m, 2 H), 3.86–3.83 (m, 1 H), 3.69–3.60 (m, 1 H), 3.48–3.38 (m, 1 H), 3.31–3.23 (m, 1 H), 2.70–2.45 (m, 4 H), 2.35–2.20 (m, 2 H), 2.18–2.05 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 136.3, 133.4, 132.0, 129.2, 128.2, 128.0, 127.7, 127.5, 127.48, 127.4, 126.0, 125.8, 125.2, 81.7, 81.68, 80.4, 80.3, 42.0, 41.9, 31.4, 31.39, 28.3, 28.26; IR (film, cm^{-1}) 3057, 1058. MS(ESI): 395.1994 (395.1987 calcd for $C_{26}H_{28}O_2$, M + Na^+).



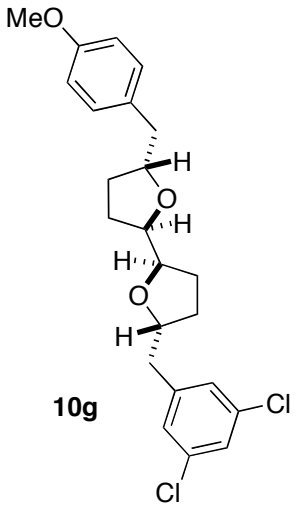
10e

(±)-(2*R,2'*R**,5*R**,5'*R**)-5-(3-Methoxybenzyl)-5'-[4-(trifluoromethyl)benzyl]octahydro-2,2'-bifuran (10e, Table 2, Entry 5).** The coupling of **18c** (40 mg, 0.15 mmol) with 4-brombenzotrifluoride (40 μL, 0.30 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 40 mg (67%) of the title compound as an orange oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.44 (m, 2 H), 7.43–7.35 (m, 2 H), 7.18 (t, *J* = 7.4 Hz, 1 H), 6.81–6.73 (m, 3 H), 4.24–4.15 (m, 2 H), 3.97–3.89 (m, 2 H), 3.78 (s, 3 H), 3.09–3.00 (m, 2 H), 2.78 (dd, *J* = 7.1, 13.7 Hz, 1 H), 2.65 (dd, *J* = 8.2, 13.3 Hz, 1 H), 1.96–1.85 (m, 4 H), 1.68–1.49 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 140.3, 139.7, 132.7, 129.2, 126.2 (q, *J* = 222.8 Hz), 125.9, 123.0, 121.7, 115.0, 111.4, 81.7, 81.5, 80.3, 79.8, 55.1, 42.0, 41.6, 31.5, 31.4, 28.3, 28.26; IR (film, cm^{-1}) 2918, 1331, 1125. MS(ESI): 443.1815 (443.1810 calcd for $C_{24}H_{27}O_3F_3$, M + Na^+).



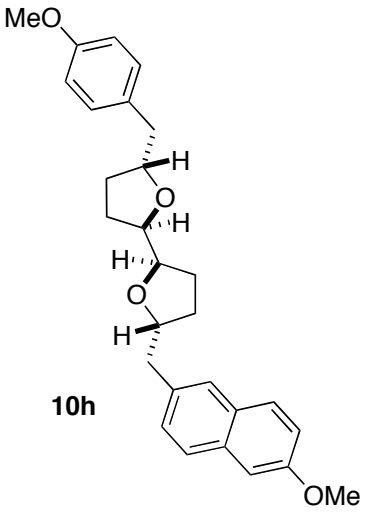
10f

(±)-(2*R,2'*R**,5*R**,5'*R**)-4-[5'-(3-Methoxybenzyl)octahydro-2,2'-bifuran-5-ylmethyl]phenyl(phenyl)methanone (10f, Table 2, Entry 6).** The coupling of **18c** (40 mg, 0.15 mmol) with 4-bromobenzophenone (80 mg, 0.30 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 46 mg (65%) of the title compound as an amber oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.77 (m, 2 H), 7.61–7.55 (m, 2 H), 7.51–7.45 (m, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 7.18 (t, *J* = 7.8 Hz, 2 H), 6.81–6.72 (m, 3 H), 4.29–4.16 (m, 2 H), 3.98–3.92 (m, 2 H), 3.78 (s, 3 H), 3.14–3.02 (m, 2 H), 2.81 (dd, *J* = 7.0, 13.3 Hz, 1 H), 2.66 (dd, *J* = 5.1, 8.2 Hz, 1 H), 1.97–1.86 (m, 4 H), 1.68–1.52 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 159.5, 144.0, 140.3, 137.8, 135.5, 132.2, 130.2, 130.0, 129.3, 129.2, 128.2, 121.7, 115.0, 111.4, 81.8, 81.6, 80.4, 79.9, 55.1, 42.0, 41.9, 31.6, 31.5, 28.3, 28.3; IR (film, cm^{-1}) 2918, 1603, 1315. MS(ESI): 479.2190 (479.2198 calcd for $C_{30}H_{32}O_4$, M + Na^+).



10g

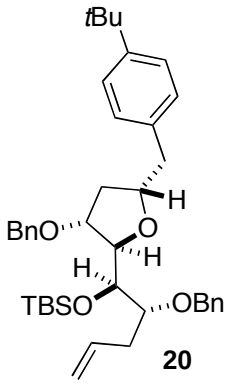
(±)-(2*R,2'*R**,5*R**,5'*R**)-5-(3,5-Dichlorobenzyl)-5'-(4-methoxybenzyl)octahydro-2,2'-bifuran (10g, Table 2, Entry 7).** The coupling of **18d** (30 mg, 0.10 mmol) with 1-bromo-3,5-dichlorobenzene (47 mg, 0.20 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 30 mg (69%) of the title compound as an amber oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.19 (m, 1 H), 7.14–7.08 (m, 4 H), 6.85–6.79 (m, 2 H), 4.20–4.10 (m, 2 H), 3.95–3.88 (m, 2 H), 3.78 (s, 3 H), 3.01–2.90 (m, 2 H), 2.71–2.59 (m, 2 H), 1.98–1.85 (m, 4 H), 1.69–1.45 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 142.3, 134.6, 130.8, 130.2, 127.8, 126.3, 113.7, 81.8, 81.5, 80.6, 79.4, 55.2, 41.2, 41.0, 31.5, 31.4, 28.3, 28.2; IR (film, cm^{-1}) 2931, 1038, 795. MS(ESI): 443.1162 (443.1157 calcd for $C_{22}H_{26}O_3Cl_2$, M + Na^+).



10h

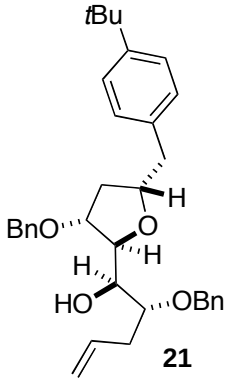
(±)-(2*R,2'*R**,5*R**,5'*R**)-5-(4-Methoxybenzyl)-5'-(6-methoxynaphthalen-2-ylmethyl)octahydro-2,2'-bifuran (10h, Table 2, Entry 8).** The coupling of **18d** (30 mg, 0.10 mmol) with 2-bromo-6-methoxynaphthalene (48 mg, 0.20 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 21 mg (52%) of the title compound as an amber oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, ($(CF_3)_2$CDOD) δ 8.32 (t, *J* = 8.4 Hz, 2 H), 8.21 (s, 1 H), 7.95 (d, *J* = 8.4 Hz, 1 H), 7.85 (s, 2 H), 7.79–7.72 (m, 2 H), 7.50 (d, *J* = 8.2 Hz, 2 H), 4.98–4.89 (m, 1 H), 4.87–4.78 (m, 1 H), 4.64–4.56 (m, 2 H), 4.45 (s, 3 H), 4.41 (s, 3 H), 3.75 (dd, *J* = 5.5, 13.1 Hz, 1 H), 3.57 (dd, *J* = 5.5, 13.3 Hz, 1 H), 3.38 (dd, *J* = 8.0, 13.1 Hz, 1 H), 3.21 (dd, *J* = 8.0, 13.3 Hz, 1 H), 2.66–2.46 (m, 4 H), 2.35–2.16 (m, 2 H), 2.15–2.05 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 157.1, 133.9, 133.0, 130.7, 130.1, 128.9, 128.4, 127.3, 126.5, 118.5, 113.5, 105.5, 81.6, 81.58, 80.5, 80.3, 55.2, 55.1, 41.7, 40.9, 31.4, 31.3, 28.2 (two carbon signals are absent due to incidental equivalence); IR (film, cm^{-1}) 2933, 1035. MS(ESI): 592.3429 (593.3427 calcd for $C_{28}H_{32}O_4$, M + Na^+).

(–)-(2*R*,2'*R*,5*R*,5'*R*)-5-(4-Methoxybenzyl)-5'-(6-methoxynaphthalen-2-ylmethyl)octahydro-2,2'-bifuran (10h, eq 4). The title compound was prepared from (–)-**12** using a sequence identical to that described above for the conversion of (±)-**12** to (±)-**17d**, (±)-**17d** to (±)-**18d**, and (±)-**18d** to (±)-**10h**. The yield of (+)-**17d** was 65%; $[\alpha]_D^{23}$ = +0.6° (*c* 0.43, CH_2Cl_2). The yield of (–)-**18d** was 88%; $[\alpha]_D^{23}$ = –3.3° (*c* 0.11, CH_2Cl_2). The yield of (–)-**10h** was 61%; $[\alpha]_D^{23}$ = –14.2° (*c* 0.12, CH_2Cl_2). NMR data for these compounds were identical to those reported above.



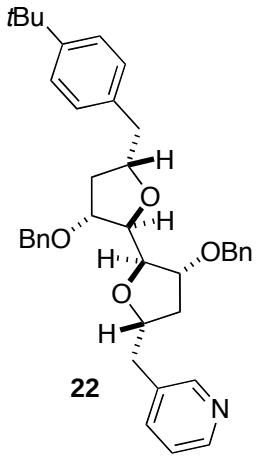
20

(–)-(1'*R*,2'*S*,2*R*,3*R*,5*S*)-2'-(Benzyloxy)-1'-[3-(benzyloxy)-5-(4-*tert*-butylbenzyl)tetrahydrofuran-2-yl]pent-4-enyloxy(*tert*-butyl)dimethylsilane (20). The coupling of **19** (40 mg, 0.8 mmol) with 4-bromo-*tert*-butylbenzene (280 μL, 1.6 mmol) was achieved following general procedure 1 using THF as solvent and a reaction temperature of 65 °C. This procedure afforded 170 mg (35%) of the title compound as an orange oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis, $[\alpha]_D^{23} = -12.2^o$ (*c* 0.37, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.26 (m, 12 H), 7.21–7.16 (m, 2 H), 6.00–5.89 (m, 1 H), 5.12–5.02 (m, 2 H), 4.61–4.54 (m, 2 H), 4.44 (d, *J* = 11.0 Hz, 1 H), 4.37 (d, *J* = 11.7 Hz, 1 H), 4.34–4.25 (m, 1 H), 4.08–4.01 (m, 2 H), 3.85 (q, *J* = 2.7 Hz, 1 H), 3.39–3.32 (m, 1 H), 3.03 (dd, *J* = 6.3, 13.3 Hz, 1 H), 2.85 (dd, *J* = 7.0, 13.7 Hz, 1 H), 2.45–2.39 (m, 2 H), 2.29–2.21 (m, 1 H), 1.84–1.74 (m, 1 H), 1.36 (s, 9 H), 0.92 (s, 9 H), 0.08 (s, 3 H), 0.01 (s, 3 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 138.7, 137.9, 136.5, 135.5, 128.9, 128.3, 128.1, 127.8, 127.6, 127.3, 125.1, 116.1, 84.2, 80.6, 80.3, 79.3, 74.6, 71.9, 71.4, 41.5, 37.6, 35.1, 34.3, 31.3, 26.0, 18.3, –4.3, –4.7; IR (film, cm^{-1}) 2955, 1092. MS(ESI): 651.3848 (651.3846 calcd for $C_{40}H_{56}SiO_4$, M + Na^+).



21

(–)-(1'*R*,2'*S*,2*S*,3*R*,5*S*)-2'-(Benzyloxy)-1'-[3-(benzyloxy)-5-(4-*tert*-butylbenzyl)tetrahydrofuran-2-yl]pent-4-en-1-ol (21). Removal of the TBS protecting group from **20** (160 mg, 0.25 mmol) with TBAF (2.5 mL, 2.5 mmol) was achieved following general procedure 2. This procedure afforded 106 mg (81%) of the title compound as an orange oil, $[\alpha]_D^{23}$ = –70.4° (*c* 0.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 12 H), 7.17–7.13 (m, 2 H), 6.01–5.88 (m, 1 H), 5.20–5.07 (m, 2 H), 4.66–4.44 (m, 4 H), 4.40–4.29 (m, 2 H), 4.21–4.15 (m, 1 H), 3.64–3.56 (m, 1 H), 3.51–3.45 (m, 1 H), 3.06 (dd, *J* = 6.6, 13.5 Hz, 1 H), 2.83 (dd, *J* = 6.5, 13.5 Hz, 1 H), 2.61–2.54 (m, 1 H), 2.48–2.39 (m, 1 H), 2.23–2.14 (m, 2 H), 1.91–1.84 (m, 1 H), 1.32 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 138.4, 138.1, 135.5, 134.9, 129.0, 128.4, 128.3, 127.9, 127.7, 127.6, 127.59, 125.3, 117.3, 82.0, 80.9, 80.4, 79.4, 72.4, 72.2, 71.8, 41.7, 37.3, 35.2, 34.4, 31.4; IR (film, cm^{-1}) 3468, 2961, 1100. MS(ESI): 537.2988 (537.2981 calcd for $C_{34}H_{42}O_4$, M + Na^+).



22

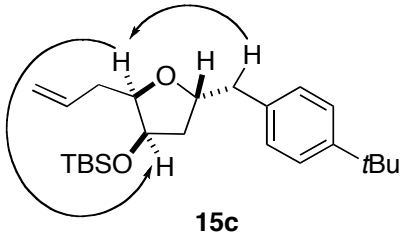
(–)-(2*R*,2'*R*,3*R*,3'*R*,5*S*,5'*S*)-3-[3,3'-Bis(benzyloxy)-5'-(4-*tert*-butylbenzyl)octahydro-2,2'-bifuran-5-ylmethyl]pyridine (22). The coupling of **21** (110 mg, 0.20 mmol) with 3-

bromopyridine (40 μL, 0.40 mmol) was achieved following general procedure 1 using toluene as solvent and a reaction temperature of 110 °C. This procedure afforded 120 mg (57%) of the title compound as an amber oil. This material was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis, $[\alpha]_D^{23} = -43.7^o$ (*c* 0.83, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43–8.36 (m, 1 H), 7.46–7.41 (m, 1 H), 7.31–7.20 (m, 11 H). 7.15–7.09 (m, 2 H), 7.07–7.02 (m, 3 H), 4.50–4.34 (m, 4 H), 4.20–4.09 (m, 3 H), 4.07–4.00 (m, 3 H), 3.00–2.89 (m, 2 H), 2.80–2.66 (m, 2 H), 2.19–2.04 (m, 2 H), 1.78–1.64 (m, 2 H), 1.25 (s, 9 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 148.9, 147.6, 138.1, 138.0, 136.8, 135.5, 134.3, 128.9, 128.44, 128.4, 127.7, 127.67, 127.6, 125.2, 123.2, 84.4, 84.2, 81.0, 80.9, 80.3, 79.6, 71.7, 41.7, 39.3, 37.3, 37.2, 34.4, 31.4 (two signals are absent due to incidental equivalence); IR (film, cm^{-1}) 2918, 1648, 1185. MS(ESI): 592.3429 (593.3427 calcd for $C_{39}H_{45}NO_4$, M + Na^+).

Assignment of Stereochemistry

2,3,5 Substituted Tetrahydrofurans (Table 1)

The relative stereochemistry of **15c** was assigned on the basis of signals observed in ^{1}H NMR nOe experiments. Relevant nOe data is shown below.

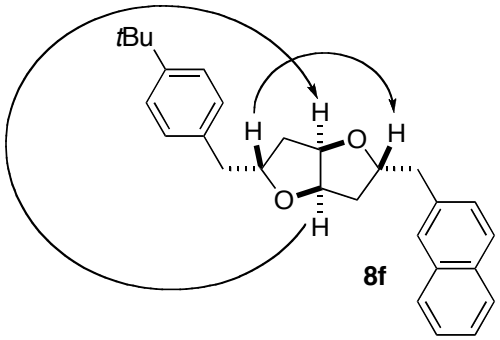


15c

The stereochemistry of the related compounds **15a**,**b**, and **d** was assigned based on analogy to **15c**.

Fused Bis-Tetrahydrofurans (Table 1)

The relative stereochemistry of **8f** was assigned on the basis of signals observed in ^{1}H NMR nOe experiments. Relevant nOe data is shown below.

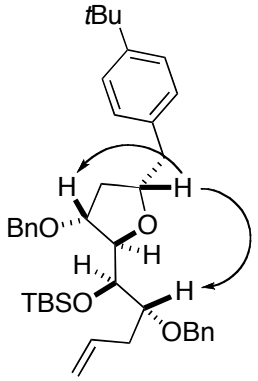


8f

The stereochemistry of the related compounds **8a–e** and **8g–h** was assigned based on analogy to **8f**.

2,5 Substituted Tetrahydrofurans (Table 2 and Scheme 2)

The relative stereochemistry of **20** was assigned on the basis of signals observed in ^{1}H NMR nOe experiments. Relevant nOe data is shown below.

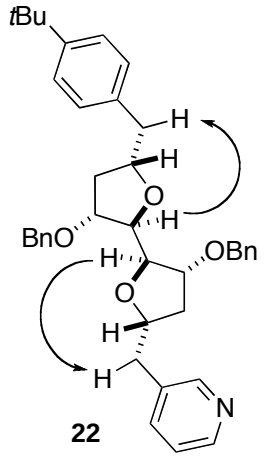


20

The stereochemistry of the related compounds **17a–d** and was assigned based on analogy to **20**.

Attached-Ring Bis-Tetrahydrofurans

The relative stereochemistry of **22** was assigned on the basis of signals observed in ^{1}H NMR nOe experiments. Relevant nOe data is shown below.



22

The stereochemistry of the related compounds **10a–h** was assigned based on analogy to **22**.

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