Palladium-Catalyzed Synthesis of 2,1'-Disubstituted Tetrahydrofurans from γ-Hydroxy Internal Alkenes. Evidence for Alkene Insertion into a Pd–O Bond and Stereochemical Scrambling via β-Hydride Elimination

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Supporting Information

Experimental procedures for synthesis of substrates, characterization data for all new compounds, descriptions of deuterium labeling experiments, and descriptions of stereochemical assignments (21 pages).

Table of Contents

General Considerations

All reactions were carried out under an argon or nitrogen atmosphere in oven- or flame-dried glassware. All catalysts and reagents were obtained from commercial sources and were used without

further purification. Compounds **1**, **2**, **3**, **4a**, and **10a** have been reported previously.[1] Toluene, THF, diethyl ether, and methylene chloride 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 and either capillary GC (known compounds) or combustion analysis (new compounds). The yields reported in the supporting information describe the result of a single experiment, whereas the yields reported in Tables 1–2 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Tables 1–2.

Preparation and Characterization of Alcohol Substrates

General Procedure 1: Addition of MeMgBr to Esters. An oven or flame dried flask was purged with argon or nitrogen and charged with MeMgBr (3 equiv, 3.0 M in diethyl ether). Additional ether was added to provide a 1.0 M solution, which was then cooled to 0°C. The appropriate ester was added dropwise via syringe and the resulting mixture was warmed to rt and stirred for 2–4 h until the starting material was found to be completely consumed as judged by TLC analysis. A solution of saturated aqueous NH_4Cl (1:1 by volume with reaction mixture) was added dropwise and the resulting mixture was then diluted with ethyl acetate (1:1 by volume with reaction mixture). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude tertiary alcohol product was then purified by flash chromatography on silica gel.

General Procedure 2: Johnson Orthoester Claisen Rearrangements.[2] A round bottom flask equipped with a short path distillation head and a recovery flask was charged with the appropriate allylic alcohol, triethyl orthoacetate (10 equiv), and pivalic acid (0.06 equiv). The mixture was heated to 100 °C with stirring for 2 h and ethanol was continuously removed by distillation. The mixture was

then heated to 140 °C for 12 h until the starting material had been completely consumed as judged by GC analysis. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (1:1 by volume). A solution of 1M aqueous HCl (1:1 by volume) was slowly added and the resulting biphasic mixture was stirred for 1 h at rt. The layers were separated and the organic layer was washed with water (2 x 50 mL), and saturated sodium bicarbonate (1 x 50 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude ester product was used without further purification.

(*Z*)-2-Methylhept-5-en-2-ol (9).[3] (*Z*)-Hex-4-enoic acid ethyl ester[4] (1.92 g, 13.5 mmol) was treated with MeMgBr (18.6 mL, 56 mmol, 3.0 M in diethyl ether) according to general procedure 1. The crude material was purified by fractional distillation (140 °C, 760 mm Hg) to afford 1.36 g (78 %) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50–5.36 (m, 2 H), 2.16–2.10 (m, 2 H), 1.62 (d, J = 6.0 Hz, 3 H), 1.55–1.51 (m, 2 H), 1.29 (s, 1 H), 1.23 (s, 6 H).

(±)-1-Cyclohex-2-enyl-2-methylpropan-2-ol (**16**). Cyclohex-2-enylacetic acid ethyl ester[5] was treated with MeMgBr (14.8 mL, 44.4 mmol, 3.0 M in diethyl ether) according to general procedure 1 to afford 1.32 g (58 %) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (m, 2 H), 2.16–2.12 (m, 1 H), 1.84–1.80 (m, 2 H), 1.74–1.68 (m, 1 H), 1.59–1.53 (m, 1 H), 1.45–1.30 (m, 3 H), 1.22–1.13 (m, 1 H), 1.11 (s, 7 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.9, 126.5, 71.4, 50.0, 31.4, 30.9, 29.9, 29.8, 24.9, 21.2; IR (film) 3368, 1147 cm^{-1}. Anal calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.57; H, 11.76.

4-Cyclohex-1-enyl-2-methylbutan-2-ol (**17**) A flame dried flask was cooled under a stream of argon and charged with diisopropyl amine (1.10 g, 10.9 mmol), DMPU (0.80 g, 6.24 mmol), and THF (3.1 mL). The mixture was cooled to 0 °C and a solution of *n*-butyllithium (6.5 mL, 10.4 mmol, 1.6 M in hexanes) was added slowly. The reaction was stirred for 30 min at 0 °C and was then cooled to –78°C, whereupon neat *tert*-butyl acetate (6.5 mL, 10.4 mmol) was added dropwise. The solution was stirred for 1 h at –78 °C, then 1-bromomethylcyclohexene[6] (2.0 g, 11.4 mmol) was added. The reaction mixture was stirred at –78 °C for 1 h and then warmed to rt with stirring over 2 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl (10 mL) and stirred for 10 minutes at rt. Ethyl acetate (20 mL) was added, 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 $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude 3-cyclohex-1-enylpropionic acid *tert*-butyl ester. Treatment of the crude ester with MeMgBr (6.3 mL, 18.9 mmol, 3.0 M in diethyl ether) following general procedure 1 afforded 0.32 g (40 % over two steps) of 4-cyclohex-1-enyl-2-methylbutan-2-ol as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44–5.40 (m, 1 H), 2.04–1.93 (m, 6 H), 1.64–1.54 (m, 7 H), 1.21 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 120.9, 120.8, 77.2, 41.5, 32.7, 29.1, 28.3, 25.2, 22.9, 22.4; IR (film) 3368, 1147 cm^{-1}. Anal calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.30; H, 12.09.

4-Cyclopent-1-enyl-2-methyl-butan-2-ol (18). 3-Iodopropionic acid ethyl ester (3.40 g, 15 mmol) was converted to the corresponding alkylzinc reagent and cross-coupled with cyclopent-1-enyl triflate[7] (2.16 g, 10 mmol) using a procedure reported by Yoshida for the cross-coupling of alkylzinc reagents with cyclohexenyl triflates.[8] This procedure afforded 670 mg (40 %) of 3-cyclopent-1-enylpropionic acid ethyl ester. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35–5.34 (m, 1 H), 4.13 (q, J = 7.0 Hz,

2 H), 2.46 (t, *J* = 7.0 Hz, 2 H), 2.40–2.36 (m, 2 H), 2.31–2.27 (m, 2 H), 2.25–2.22 (m, 2 H), 1.85 (p, *J* = 7.0 H, 2 H), 1.25 (t, *J* = 7.0 Hz, 3 H).

3-Cyclopent-1-enylpropionic acid ethyl ester (670 mg, 3.98 mmol) was treated with MeMgBr (4.0 mL, 12.0 mmol, 3.0 M in diethyl ether) according to general procedure 1 to afford 345 mg (56 %) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36–5.33 (m, 1 H), 2.29–2.22 (m, 4 H), 2.14–2.11 (m, 2 H), 1.83 (p, *J* = 8.0 Hz, 2 H), 1.64–1.60 (m, 2 H), 1.47 (s, 1 H), 1.21 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 123.1, 70.9, 41.5, 35.1, 32.3, 29.1, 25.9, 23.3; IR (film) 3368 cm^{-1}. MS (EI) *m/z* 154.1360 (154.1360 calcd for $C_{10}H_{18}O$).

Characterization Data for Tetrahydrofuran Products

(±)-(4R,5R)-4-Biphenyl-4-yl-5-ethyl-2,2-dimethyltetrahydrofuran (4b). This compound was isolated from the mixture of **4a**, **4b**, and **4c** by preparative HPLC and was obtained as a ~5:1 mixture of **4b** and **4c**. Data are given for **4b**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 2 H), 7.55 (d, *J* = 8.0 Hz, 2 H), 7.44 (t, *J* = 8.0 Hz, 2 H), 7.36–7.31 (m, 3 H), 3.93 (ddd, *J* = 4.0, 6.2, 10.0 Hz, 1 H), 3.11 (ddd, *J* = 8.0, 9.7, 11.5 Hz, 1 H), 2.25 (dd, *J* = 8.0, 12.5 Hz, 1 H), 2.05 (t, *J* = 11.5 Hz, 1 H), 1.66–1.60 (m, 1 H), 1.55–1.48 (m, 1 H), 1.47 (s, 3 H), 1.34 (s, 3 H), 0.92 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 140.1, 139.4, 128.7, 128.1, 127.2, 127.1, 126.9, 85.9, 79.5, 50.5, 48.6, 29.6, 29.4, 26.7, 10.1. MS (EI) *m/z* 280.1827 (280.1827 calcd for $C_{20}H_{24}O$).

The structure of isomer **4c** was assigned based on comparison of the literature ^{1}H and ^{13}C NMR data for the closely related compound 2,2-dimethyl-5-phenethyltetrahydrofuran[9] to the additional signals present in the ^{1}H and ^{13}C NMR spectra of the **4b**/**4c** mixture.

(±)–(1'*S*,5*R*)-2,2-Dimethyl-5-(1'-*o*-tolylethyl)tetrahydrofuran (11a). Reaction of (*E*)-2-methylhept-5-en-2-ol (64 mg, 0.5 mmol) with 2-bromotoluene (171 mg, 1.0 mmol) following the general procedure afforded 94 mg (86 %) of the title compound as a pale yellow oil. This material was obtained as a ca. 6:1 mixture of diastereomers as judged by ^{1}H NMR analysis (the crude reaction mixture contained a 3:1 mixture of diastereomers). Data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.10 (m, 4 H), 4.17–4.11 (m, 1 H), 3.23 (p, *J* = 6.4 Hz, 1 H), 2.38 (s, 3 H), 1.91–1.80 (m, 1 H), 1.79–1.73 (m, 1 H), 1.72–1.65 (m, 2 H), 1.29–1.22 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 135.9, 130.0, 126.4, 125.8, 125.7, 81.8, 80.2, 38.8, 38.6, 28.7, 28.4, 28.0, 19.8, 15.9; IR (film) 1364 cm^{-1}. Anal calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found C, 82.72; H, 9.86.

(±)–(1'*S*,5*R*)-5-[1-Naphthalen-1-ylethyl]-2,2-dimethyltetrahydrofuran (12a). Reaction of (*E*)-2-methylhept-5-en-2-ol (64 mg, 0.5 mmol) with 1-bromonaphthalene (207 mg, 1.0 mmol) following the general procedure afforded 97 mg (83 %) of the title compound as a pale yellow oil. This material was obtained as a ca. 10:1 mixture of diastereomers as judged by ^{1}H NMR analysis (the crude reaction mixture contained a 5:1 mixture of diastereomers). Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.5 Hz, 1 H), 7.89 (d, *J* = 8.0 Hz, 1 H), 7.76 (d, *J* = 7.5 Hz, 1 H), 7.58–7.49 (m, 4 H), 4.45–4.41 (m, 1 H), 3.98 (p, *J* = 7.0 Hz, 1 H), 1.88–1.81 (m, 1 H), 1.79–1.72 (m, 1 H), 1.71–1.63 (m, 2 H), 1.45 (d, *J* = 6.5 Hz, 3 H), 1.30 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 134.0, 132.2, 129.0, 126.8, 125.9, 125.6, 125.3, 124.0, 123.6, 81.6, 80.8, 38.8, 37.7, 28.9, 28.1, 28.0, 15.5; IR (film) 1364 cm^{-1}. Anal calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found C, 85.06; H, 8.59.

(±)-(1'*R*,5*R*)-5-[1'-(4-*tert*-Butylphenyl)ethyl]-2,2-dimethyltetrahydrofuran (13a). Reaction of (*Z*)-2-methylhept-5-en-2-ol (32 mg, 0.25 mmol) with 1-bromo-4-*tert*-butylbenzene (107 mg, 0.5

mmol) following the general procedure afforded 45 mg (74 %) of the title compound as a pale yellow oil. This material was obtained as a ca. 5:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.5 Hz, 2 H), 7.12 (d, *J* = 8.5 Hz, 2 H), 4.04–3.99 (m, 1 H), 2.71–2.68 (m, 1 H), 1.72–1.68 (m, 1 H) 1.64–1.55 (m, 3 H), 1.32 (d, *J* = 8.5 Hz, 3 H), 1.31 (m, 9 H), 1.23 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8, 141.4, 127.4, 124.9, 83.5, 80.7, 45.4, 38.2, 31.3, 31.3, 30.1, 29.1, 28.2, 18.7; IR (film) 1363 cm^{-1}. Anal calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.42; H, 10.57.

(±)-(1'*R*,5*R*)-5-[1'-(3-Methoxyphenyl)ethyl]-2,2-dimethyltetrahydrofuran (14a). Reaction of (*Z*)-2-methylhept-5-en-2-ol (64 mg, 0.5 mmol) with 3-bromoanisole (187 mg, 1.0 mmol) following the general procedure afforded 93 mg (79 %) of the title compound as a pale yellow oil. This material was obtained as a ca. 7:1 mixture of diastereomers as judged by ^{1}H NMR analysis (the crude reaction mixture contained a 5:1 mixture of diastereomers). Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.5 Hz, 1 H), 6.82–6.75 (m, 3 H), 4.06–4.02 (m, 1 H), 3.81 (s, 3 H), 2.71 (p, *J* = 7.5 Hz, 1 H), 1.76–1.71 (m, 1 H), 1.63–1.56 (m, 3 H), 1.35 (d, *J* = 7.0 Hz, 3 H), 1.25 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 146.2, 129.0, 120.3, 113.8, 111.1, 83.2, 80.7, 55.0, 46.0, 38.2, 30.0, 29.0, 28.1, 18.8; IR (film) 1363 cm^{-1}. Anal calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.71; H, 9.56.

(±)-(1'*R*,5*R*)-2,2-Dimethyl-5-(1'-*o*-tolylethyl)tetrahydrofuran (15a). Reaction of (*Z*)-2-methylhept-5-en-2-ol (64 mg, 0.5 mmol) with 2-bromotoluene (171 mg, 1.0 mmol) following the general procedure afforded 60 mg (55 %) of the title compound as a pale yellow oil. This material was obtained as a ca. 3:1 mixture of diastereomers as judged by ^{1}H NMR analysis (the crude reaction mixture contained a 2:1 mixture of diastereomers). Data are for the major diastereomer. ^{1}H NMR (500

MHz, $CDCl_3$) δ 7.30–7.07 (m, 4 H), 4.18–4.13 (m, 1 H), 3.02 (q, *J* = 6.5 Hz, 1 H), 2.37 (s, 3 H), 1.81–1.76 (m, 1 H), 1.69–1.64 (m, 2 H), 1.54–1.48 (m, 1 H), 1.30 (d, *J* = 7.0 Hz, 3 H), 1.27 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 135.5, 130.1, 126.3, 125.9, 125.6, 83.6, 80.8, 40.6, 38.3, 30.2, 29.2, 28.2, 20.1, 19.1; IR (film) 1364 cm^{-1}. Anal calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.60; H, 10.05.

(±)-(3a*R*,6a*S*,6*S*)-[4-(2,2-Dimethylhexahydrocyclopenta[*b*]furan-6-yl)phenyl]dimethylamine (19). Reaction of 1-cyclopent-2-enyl-2-methylpropan-2-ol (70 mg, 0.5 mmol) with 4-bromo-*N*,*N*-dimethylaniline (200 mg, 1.0 mmol) following the general procedure afforded 76 mg (59 %) of the title compound as a viscous, pale yellow oil. This material was obtained with dr ≥ 20:1 as judged by ^1H NMR analysis. ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 11.0 Hz, 2 H), 6.69 (d, *J* = 11.0 Hz, 2 H), 4.41 (t, *J* = 7.5 Hz, 1 H), 2.88–2.83 (m, 7 H), 2.71–2.64 (m, 1 H), 2.07 (dd, *J* = 11.5, 15.0 Hz, 1 H), 2.00–1.90 (m, 1 H), 1.75–1.61 (m, 2 H), 1.51 (dd, *J* = 7.5, 15.5 Hz, 1 H), 1.32–1.27 (m, 4 H), 1.09 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 129.5, 128.7, 112.7, 84.1, 81.0, 50.6, 47.4, 43.2, 40.8, 32.0, 29.2, 27.7, 25.3; IR (film) 1365 cm^{-1}. Anal calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.99; H, 9.75; N, 5.36.

(±)-(3a*R*,6a*S*,6*S*)-4-(2,2-Dimethylhexahydrocyclopenta[*b*]furan-6-yl)isoquinoline (20). Reaction of 1-cyclopent-2-enyl-2-methylpropan-2-ol (35 mg, 0.25 mmol) with 4-bromoisoquinoline (104 mg, 0.5 mmol) using 5 mol % xantphos (7.2 mg, 0.0125 mmol) in place of P(*o*-tol)$_3$ following the general procedure afforded 49 mg (73 %) of the title compound as a viscous, brown oil. This material was obtained with dr ≥ 20:1 as judged by ^1H NMR analysis. ^1H NMR (500 MHz, $CDCl_3$) δ 9.11 (s, 1 H), 8.53 (s, 1 H), 8.09 (d, *J* = 8.5 Hz, 1 H), 7.94 (d, *J* = 8.5 Hz, 1 H), 7.68 (t, *J* = 7.5 Hz, 1 H), 7.55 (t,

J = 7.0 Hz, 1 H), 4.72 (t, J = 6.0 Hz, 1 H), 3.47 (dt, J = 5.0, 13.0 Hz, 1 H), 3.03 (p, 8.5 Hz, 1 H), 2.36–2.31 (m, 1 H), 2.12 (dd, J = 9.5, 12.5 Hz, 1 H), 1.85–1.76 (m, 2 H), 1.68–1.66 (m, 1 H), 1.36 (dd, J = 8.0, 12.2 Hz, 1 H), 1.23 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 142.8, 134.8, 129.8, 128.6, 128.3, 128.2, 126.2, 122.3, 82.9, 81.4, 47.0, 44.9, 43.4, 31.6, 27.5, 27.0, 25.3; IR (film) 1366 cm^{-1}. Anal calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 81.06; H, 7.91; N, 5.12.

(±)-(3a*R*,7a*S*,7*S*)-7-(4-*tert*-butylphenyl)-2,2-dimethyloctahydrobenzofuran (21). Reaction of 1-cyclohex-2-enyl-2-methylpropan-2-ol (39 mg, 0.25 mmol) with 1-bromo-4-*tert*-butylbenzene (107 mg, 0.5 mmol) following the general procedure afforded 45 mg (63 %) of the title compound as a colorless oil. This material was obtained with dr ≥ 20:1 as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 4 H), 4.09 (t, J = 3.0 Hz, 1 H), 2.76 (dt, J = 3.0, 12.5 Hz, 1 H), 2.09–2.06 (m, 1 H), 1.86 (dd, J = 7.0, 12.2 Hz, 1 H), 1.83–1.78 (m, 2 H), 1.69–1.66 (m, 1 H), 1.54–1.53 (m, 1 H), 1.48–1.37 (m, 2 H), 1.35–1.33 (m, 4 H), 1.30 (s, 9 H), 1.15 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 141.8, 127.6, 124.8, 78.9, 78.2, 45.2, 44.8, 40.6, 34.2, 31.3, 30.6, 29.3, 28.4, 26.9, 25.9; IR (film) 1364 cm^{-1}. Anal calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56;. Found: C, 83.68; H, 10.30.

(±)-(3a*R*,7a*S*,7*S*)-4-(2,2-Dimethyloctahydrobenzofuran-7-yl)benzonitrile (22). Reaction of 1-cyclohex-2-enyl-2-methylpropan-2-ol (39 mg, 0.25 mmol) with 4-bromobenzonitrile (91 mg, 0.5 mmol) following the general procedure using xantphos in place of P(*o*-tol)$_3$ afforded 45 mg (63 %) of the title compound as a pale yellow oil. This material was obtained with dr ≥ 20:1 as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 2 H), 7.47 (d, J = 8.0 Hz, 2 H), 4.00 (t, J = 3.0 Hz, 1 H), 2.83 (dt, J = 3.5, 12.5 Hz, 1 H), 2.12–2.07 (m, 1 H), 1.89–1.79 (m, 3 H),

1.64–1.55 (m, 2 H), 1.51–1.40 (m, 2 H), 1.37–1.33 (m, 4 H), 1.10 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 131.7, 129.0, 119.3, 109.5, 79.2, 77.5, 45.7, 45.1, 40.5, 30.5, 29.2, 28.2, 26.4, 25.5; IR (film) 1365 cm^{-1}. Anal calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.89; H, 8.24; N, 5.58.

(±)-*E*-(3a*R*,7a*S*,7*S*)-2,2-Dimethyl-7-(β-styryl)octahydrobenzofuran (23). Reaction of 1-cyclohex-2-enyl-2-methylpropan-2-ol (77 mg, 0.5 mmol) with β-bromostyrene (183 mg, 1.0 mmol) following the general procedure afforded 91 mg (71 %) of the title compound as a brown oil. This material was obtained with dr ≥ 20:1 as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.0 Hz, 2 H), 7.28 (t, *J* = 7.5 Hz, 2 H), 7.17 (t, *J* = 7.5 Hz, 1 H), 6.41–6.40 (m, 2 H), 3.90 (t, *J* = 3.5 Hz, 1 H), 2.42–2.38 (m, 1 H), 2.15–1.96 (m, 1 H), 1.87 (dd, *J* = 7.5, 12.5 Hz, 1 H), 1.74–1.72 (m, 1 H), 1.56–1.48 (m, 4 H), 1.37 (s, 3 H), 1.34–1.28 (m, 2 H), 1.19 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 134.0, 128.8, 128.3, 126.6, 126.1, 78.8, 78.4, 45.3, 43.5, 39.9, 30.6, 29.3, 28.3, 26.5, 25.1; IR (film) 1365 cm^{-1}. Anal calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.44;. Found: C, 84.39; H, 9.34.

(±)-(1*R*,6*S*)-6-(4-*tert*-Butylphenyl)-2',2'-dimethyl-1-oxaspiro[4.5]decane (24). Reaction of 4-cyclohex-1-enyl-2-methylbutan-2-ol (42 mg, 0.25 mmol) with 1-bromo-4-*tert*-butylbenzene (107 mg, 0.5 mmol) following the general procedure afforded 49 mg (65 %) of the title compound as a pale yellow oil. This material was obtained with dr ≥ 20:1 as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.25 (m, 4 H), 2.43 (dd, *J* = 3.5, 13.0 Hz, 1 H), 2.08 (dq, *J* = 3.7, 13.0 Hz, 1 H), 1.88–1.76 (m, 4 H), 1.63–1.58 (m, 3 H), 1.52–1.37 (m, 3 H), 1.33 (s, 9 H), 1.21 (s, 3 H), 0.95 (s, 3 H), 0.79–0.74 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8, 140.3, 129.5, 124.0, 84.2, 80.9, 52.2, 40.5,

37.4, 36.2, 34.3, 31.4, 29.8, 29.6, 28.5, 26.5, 22.5; IR (film) 1362 cm^{-1}. Anal calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73;. Found: C, 84.32; H, 10.88.

(±)-(1*R*,6*S*)-[4-(2',2'-Dimethyl-1-oxaspiro[4.5]dec-6-yl)phenyl]phenylmethanone (25). Reaction of 4-cyclohex-1-enyl-2-methylbutan-2-ol (42 mg, 0.25 mmol) with 4-bromobenzophenone (131 mg, 0.5 mmol) following the general procedure afforded 30 mg (34 %) of the title compound as a pale yellow oil. This material was obtained with dr ≥ 20:1 as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.5 Hz, 2 H), 7.72 (d, *J* = 8.5 Hz, 2 H), 7.57 (t, *J* = 7.5 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 2 H), 7.43 (d, *J* = 7.0 Hz, 2 H), 2.54 (dd, *J* = 3.5, 12.7 Hz, 1 H), 2.09 (dq, *J* = 4.0, 13.0 Hz, 1 H), 1.89–1.83 (m, 1 H), 1.83–1.74 (m, 3 H), 1.66–1.59 (m, 3 H), 1.59–1.51 (m, 1 H), 1.45–1.33 (m, 2 H), 1.20 (s, 3 H), 0.94 (s, 3 H), 0.86–0.81 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 148.8, 137.9, 135.3, 132.0, 129.9, 129.3, 128.1, 83.4, 81.0, 52.9, 40.2, 37.4, 36.1, 29.8, 29.5, 28.6, 26.2, 22.3 (two aromatic signals are incidentally equivalent); IR (film) 1659, 1363 cm^{-1}. Anal calcd for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10. Found: C, 82.72; H, 8.17.

(±)-*E*-(1*R*,6*S*)-2',2'-Dimethyl-6-(β-styryl)-1-oxaspiro[4.5]decane (26). Reaction of 4-cyclohex-1-enyl-2-methylbutan-2-ol (42 mg, 0.25 mmol) with β-bromostyrene (92 mg, 0.5 mmol) following the general procedure afforded 43 mg (64 %) of the title compound as a brown oil. This material was obtained with dr ≥ 20:1 as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 9.0 Hz, 2 H), 7.29 (t, *J* = 8.0 Hz, 2 H), 7.18 (t, *J* = 7.5 Hz, 1 H), 6.35 (d, *J* = 16.0 Hz, 1 H), 6.28 (dd, *J* = 8.5, 16.2 Hz, 1 H), 2.08–2.02 (m, 2 H), 1.81–1.59 (m, 8 H), 1.54–1.49 (m, 2 H), 1.33–1.28 (m, 1 H), 1.26 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 133.2, 129.8, 128.5, 126.7, 125.9, 83.8, 80.9, 50.3, 39.2, 37.9, 36.3, 30.0, 29.7, 28.9, 25.1, 22.4; IR (film) 1363 cm^{-1}.

Anal calcd for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.50; H, 10.03.

Assignment of Stereochemistry

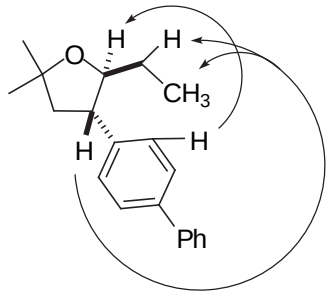
1',2-Disubstituted Tetrahydrofurans

The stereochemical assignment of **4a** and **10a** has been previously described in the supporting information for the preliminary communication of these studies.[1] The stereochemistry of **11a–15a** was assigned by comparison of ^{1}H and ^{13}C NMR spectra obtained for **11a–15a** to the NMR data obtained for the major and minor diastereomers of **4a** and **10a**.

2-Ethyl-3-aryl Tetrahydrofurans (Regioisomeric Side Products)

The stereochemistry of **4b** was assigned on the basis of the nOe signals shown below. The stereochemistry of the analogous regioisomeric products **11b–15** was assigned based on analogy to **4b**.

4b

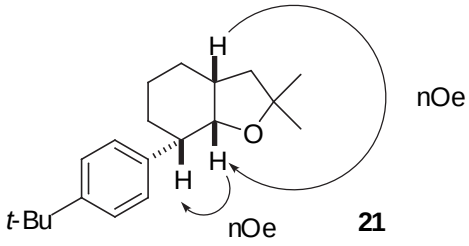


Octahydrocyclopenta[*b*]furans

The stereochemical assignment of **2** has been previously has been previously described in the supporting information for the preliminary communication of these studies.[1] The relative stereochemistry of **19** and **20** was assigned by comparison of ^{1}H and ^{13}C NMR spectra obtained for **19–20** to the NMR data obtained for **2**.

Octahydrobenzofurans

The relative stereochemistry of **21** was assigned on the basis of nOe signals between the C3a, C7a, and C7 hydrogens as illustrated below.

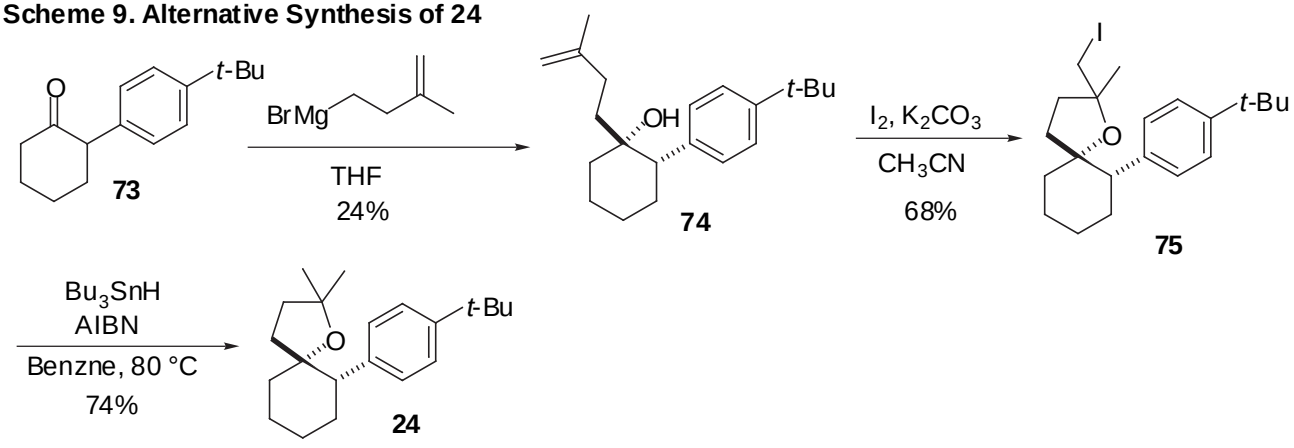


The relative stereochemistry of the octahydrobenzofuran products **22** and **23** were assigned based on analogy with this molecule.

Oxaspiro[4.5]decanes

The relative stereochemistry of **24** was determined by comparing the ^{1}H NMR spectrum of this compound to that obtained from a different sample of **24** prepared using the synthetic route illustrated in Scheme 9. The relative stereochemistry of **25** and **26** was assigned based on analogy with this molecule.

Scheme 9. Alternative Synthesis of 24



(±)-(1*R*,6*S*)-6-(4-*tert*-Butylphenyl)-2',2'-dimethyl-1-oxaspiro[4.5]decane (Prepared as shown above in Scheme 9) (24). A flame dried flask was cooled under a stream of argon and charged with Mg turnings (1.08 g, 44.8 mmol). THF (11 mL) was added, and the suspension was cooled to 0 °C. Neat 1-bromo-3-methylbut-3-ene[10] (1.67 g, 11.2 mmol) was added dropwise to the suspension, and the resulting solution was warmed to rt with stirring for 1.5 h. The reaction mixture was transferred to a dry, argon filled flask via cannula and additional THF (11 mL) was added by syringe. A solution of 2-(4-*tert*-butylphenyl)cyclohexanone (**73**)[11] (1.30 g, 5.60 mmol) in THF (4 mL) was added, the resulting solution was stirred at rt for 8 h, and then saturated aqueous NH_4Cl (20 mL) was added dropwise. The resulting mixture was diluted with ethyl acetate (40 mL) and the aqueous layer was removed and extracted with ethyl acetate (2 x 20 mL). The organic layers were combined and dried over anhydrous Na_2SO_4, decanted, and concentrated *in vacuo*. The crude material was obtained as an 8:1 mixture of diastereomers as determined by ^{1}H NMR analysis. The diastereomers were separated by flash chromatography on silica gel (19:1 hexanes/ethyl acetate) to afford 804 mg (24 %) of (**74**). The relative stereochemistry was assigned by comparison of NMR spectral data to those previously reported for the related compound (1*S*,2*R*)-1-allyl-2-phenylcyclohexanol.[12] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8 Hz, 2 H), 7.18 (d, *J* = 8 Hz, 2 H), 4.61 (s, 1 H), 4.55 (s, 1 H), 2.55 (dd, *J* = 3.2, 13.0 Hz, 1 H), 2.12–2.01 (m, 2 H), 1.99–1.91 (m, 1 H), 1.87–1.82 (m, 2 H), 1.81 (s, 1 H), 1.74–1.67 (m, 1 H), 1.62 (m, 5 H), 1.46–1.37 (m, 4 H), 1.35 (s, 9 H).

A flame dried flask was cooled under a stream of argon and charged with (**74**) (310 mg, 1.03 mmol), potassium carbonate (184 mg, 1.34 mmol), and acetonitrile (13 mL). Iodine (1.72 g, 6.78 mmol) was added and the solution was stirred at rt until the starting material had been completely consumed as judged by TLC analysis (~3 h). Water (20 mL) and methylene chloride (40 mL) were added to the reaction mixture and the layers were separated. The organic layer washed with water (2 x

20 mL) and saturated aqueous Na_2SO_3 (1 x 20 mL), and then was dried over anhydrous $MgSO_4$, decanted, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (49:1 hexanes/ethyl acetate) to afford 299 mg (68 %) of **75** as a 2:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data is for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.0 Hz, 2 H), 7.18 (d, J = 8.0 Hz, 2 H), 3.25 (d, J = 9.6 Hz, 0.67 H), 3.18 (d, J = 9.6 Hz, 0.67 H), 2.84 (d, J = 9.6 Hz, 0.33 H), 2.61 (d, J = 9.2 Hz, 0.33 H), 2.45–2.37 (m, 1 H), 2.11–2.00 (m, 1 H), 1.88–1.67 (m, 4 H), 1.60–1.44 (m, 3 H), 1.44–1.43 (m, 1 H), 1.34–1.31 (m, 1 H), 1.30 (s, 9 H), 1.25–1.22 (m, 1 H), 1.06 (s, 3 H), 0.88–0.81 (m, 1 H).

A flame dried flask was cooled under a stream of argon and charged with (**75**) (299 mg, 0.70 mmol), AIBN (5.7 mg, 0.035 mmol), and benzene (2.3 mL). Tributyltin hydride (235 mg, 0.84 mmol) was added, and the reaction mixture was heated to reflux. The starting material was consumed after 3 h as judged by capillary GC analysis, and the reaction mixture was concentrated *in vacuo*. The crude product was dissolved in diethyl ether (10 mL) and treated with a solution saturated aqueous potassium fluoride (10 mL). The resulting biphasic solution was stirred at rt for 2 h, then the aqueous layer was separated and extracted with diethyl ether (2 x 20 mL). The organic layers were combined and dried over anhydrous $MgSO_4$, decanted, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (19:1 hexanes/ethyl acetate) to afford 155 mg (74 %) of (±)-(1*R*,6*S*)-6-(4-*tert*-Butylphenyl)-2',2'-dimethyl-1-oxaspiro[4.5]decane (**24**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.25 (m, 4 H), 2.43 (dd, J = 3.5, 13.0 Hz, 1 H), 2.08 (dq, J = 3.7, 13.0 Hz, 1 H), 1.88–1.76 (m, 4 H), 1.63–1.58 (m, 3 H), 1.52–1.37 (m, 3 H), 1.33 (s, 9 H), 1.21 (s, 3 H), 0.95 (s, 3 H), 0.79–0.74 (m, 1 H).

Deuterium Labeling Studies (eq 3–5)

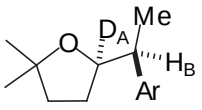
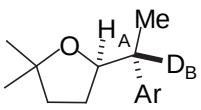
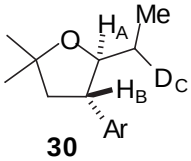
(*E*)-5-Deuterio-2-methylhept-5-en-2-ol (27). A flame dried flask equipped with a reflux condenser was cooled under a stream of argon and charged with $LiAlD_4$ (50 mL, 50 mL, 1.0 M in THF). But-3-yn-2-ol (1.75 g, 25 mmol) was added and the mixture was heated to reflux for 20 h. The reaction was monitored by ^{1}H NMR, and upon consumption of the starting material the reaction was carefully quenched by slowly adding water (2.2 mL), NaOH (2.2 mL, 10 M), and additional water (6.6 mL). The resulting suspension was decanted and the solvent was removed by fractional distillation to afford 3-deuteriobut-3-en-2-ol as a 2:1 mixture of the title compound and THF. This material was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21–5.19 (m, 1 H), 5.06–5.05 (m, 1 H), 4.30 (q, *J* = 6.0 Hz, 1 H), 1.52 (s, 1 H), 1.27 (d, *J* = 6.4 Hz, 3 H).

The crude 3-deuteriobut-3-en-2-ol described above was treated with triethyl orthoacetate using general procedure 2 to afford 391 mg (7 % over two steps) of (*E*)-4-deuteriohex-4-enoic acid ethyl ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48–5.45 (m, 1 H), 4.12 (q, *J* = 6.0 Hz, 2 H), 2.36–2.30 (m, 2 H), 2.30–2.27 (m, 2 H), 1.63 (d, *J* = 6.8 Hz, 3 H), 1.24 (t, *J* = 6.0 Hz, 3 H).

(*E*)-4-Deuteriohex-4-enoic acid ethyl ester (391 mg, 2.73 mmol) was treated with MeMgBr (2.7 mL, 8.1 mmol, 3.0 M in diethyl ether) according to general procedure 1 to afford 200 mg (57 %) of the title compound as a colorless oil. This material was found to contain ≥95% D incorporation at C-5 as judged by ^{1}H and ^{13}C NMR and MS analysis**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46–5.44 (m, 1 H), 2.08–2.04 (m, 2 H), 1.64 (d, *J* = 5.2 Hz, 3 H), 1.55–1.51 (m, 2 H), 1.28 (s, 1 H), 1.21 (s, 6 H); ^{2}H NMR (83 MHz, $CHCl_3$) δ 5.42 (s, 1 D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.0 (t, J_{CD} = 22.7 Hz), 124.6, 70.8, 43.3, 29.1, 27.3, 17.7; IR (film) 3359 cm^{-1}; MS (EI) *m/z* 111.1160 (111.1157 calcd for $C_8H_{15}DO$, M–H_2O).

Palladium-Catalyzed Reaction of (*E*)-5-Deuterio-2-methylhept-5-en-2-ol with 4-Bromobiphenyl (eq 3). Reaction of 32 mg (0.25 mmol) (*E*)-5-deuterio-2-methylhept-5-en-2-ol with 4-bromobiphenyl (117 mg, 0.5 mmol) according to the general procedure afforded 35 mg (50 %) of deuterated (±)-(1'*S*,5*R*)-5-[1'-(4-phenyl)phenylethyl]-2,2-dimethyltetrahydrofuran-D-1 The material was isolated as a ca. 79:17:4 mixture of **28**:**29**:**30** as judged by ^{1}H NMR analysis; all isomers contained a single deuterium atom as judged by MS analysis. The major diastereomer **28** was found to be deuterated at C5 (94%D), the minor diastereomer **29** was mainly deuterated at C1' (62%D), and the minor 3-aryl regioisomer **30** was deuterated at C1'. Complete data are given for the major diastereomer (**28**); selected data are shown below for the minor isomers (Table 3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 7.0 Hz, 2 H), 7.59 (d, J = 8.0 Hz, 2 H), 7.48–7.35 (m, 5 H), 2.94 (q, J = 6.8 Hz, 1 H), 1.92–1.86 (m, 1 H), 1.79–1.72 (m, 1 H), 1.68–1.56 (m, 2 H), 1.31 (d, J = 7.2 Hz, 3 H), 1.22 (s, 6 H); ^{2}H NMR (83 MHz, $CHCl_3$) δ 4.16 (s, 1 D); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 141.1, 138.9, 128.6, 128.5, 126.9, 126.8, 126.7, 82.5 (t, J_{CD} = 19.2 Hz), 80.5, 43.7, 38.4, 28.7, 28.3, 28.0, 16.4; IR (film) 1363 cm^{-1}. MS (EI) *m/z* 281.1886 (281.1889 calcd for $C_{20}H_{23}DO$).

Table 3. Selected NMR Data for the mixture of 28, 29, and 30

	 **28**		 **29**		 **30**		
	δ 4.16 (D_A/H_A)	2.94 (H_B/D_B)	4.07 (H_A/D_A)	2.80 (D_B/H_B)	3.94 (H_A/D_A)	3.12 (H_B/D_B)	1.65 (D_C/H_C)
^{1}H NMR Integral Area	7	100	16	7	5	8	ND
^{2}H NMR Integral Area	100	3	7	12	0	0	2

(*E*)-6-Deuterio-2-methylhept-5-en-2-ol (31). A flame-dried flask was cooled under a stream of argon and charged with $LiAlD_4$ (1.41 g, 35 mmol) and diethyl ether (20 mL). The mixture was cooled to 0 °C and methyl vinyl ketone (2.03 g, 29 mmol) in diethyl ether (5 mL) was added dropwise. The solution was warmed to rt over 8 h and monitored by ^{1}H NMR. Upon consumption of the starting material the reaction was carefully quenched by slowly adding water (2 mL), NaOH (2 mL, 10 M), and additional water (5 mL). The resulting suspension was decanted and the solvent was removed by fractional distillation to provide 1.37 g (65 %) of 2-deuteriobut-3-en-2-ol as a clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (dd, J = 11.6, 16.8 Hz, 1 H), 5.16 (dd, J = 1.6, 17.2 Hz, 1 H), 5.01 (dd, J = 1.6, 10.8 Hz, 1 H), 1.42 (s, 1 H), 1.20 (s, 3 H).

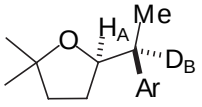
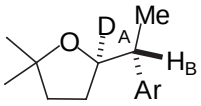
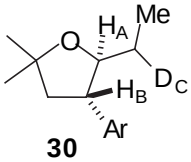
2-Deuteriobut-3-en-2-ol (1.20 g, 16 mmol) was treated with triethylorthoacetate according to general procedure 2 to afford 1.07 g (46 %) of (*E*)-5-deuteriohex-4-enoic acid ethyl ester as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42–5.39 (m, 1 H), 4.12 (q, J = 7.0 Hz, 2 H), 2.36–2.32 (m, 2 H), 2.31–2.27 (m, 2 H), 1.63 (s, 3 H), 1.24 (t, J = 7.0 Hz, 3 H).

(*E*)-5-Deuteriohex-4-enoic acid ethyl ester (1.07 g, 7.5 mmol) was treated with MeMgBr (7.5 mL, 22.5 mmol, 3.0 M in diethyl ether) according to general procedure 1 to afford 460 mg (47 %) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42–5.35 (m, 1 H), 2.03–1.99 (m, 2 H), 1.78 (s, 1 H), 1.58 (s, 3 H), 1.49–1.45 (m, 2 H), 1.15 (s, 6 H); ^{2}H NMR (83 MHz, $CHCl_3$) δ 5.45 (s, 1 D); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.2, 124.3 (t, J_{CD} = 17.8 Hz), 70.7, 43.3, 29.0, 27.4, 17.6; IR (film) 3368 cm^{-1}; MS (EI) *m/z* 111.1153 (111.1157 calcd for $C_8H_{15}DO$, M–H_2O).

Palladium-Catalyzed Reaction of (*E*)-6-Deuterio-2-methylhept-5-en-2-ol with 4-bromobiphenyl (eq 4). Reaction of 64.5 mg (0.5 mmol) (*E*)-6-deuterio-2-methylhept-5-en-2-ol with 4-bromobiphenyl (233 mg, 1.0 mmol) according to the general procedure afforded 93 mg (66 %) of

(±)-(1'*S*,5*R*)-5-[1'-(4-Phenyl)phenylethyl]-2,2-dimethyltetrahydrofuran-D-1. The material was isolated as a ca. 75:20:5 mixture of **32**:**33**:**30** as judged by ^{1}H NMR analysis; all isomers contained a single deuterium atom as judged by MS analysis. The major diastereomer **32** was found to be deuterated at C1' (95%D), the minor diastereomer **33** was mainly deuterated at C5 (78%D), and the minor 3-aryl regioisomer **32** was deuterated at C1'. Complete data are given for the major diastereomer; selected data are shown below for the minor isomers (Table 4). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 7.5 Hz, 2 H), 7.52 (d, J = 8.0 Hz, 2 H), 7.42 (t, J = 8.0 Hz, 2 H), 7.33–7.30 (m, 3 H), 4.16 (t, J = 7.5 Hz, 1 H), 1.91–1.85 (m, 1 H), 1.79–1.72 (m, 1 H), 1.68–1.54 (m, 2 H), 1.30 (s, 3 H), 1.21 (s, 6 H); ^{2}H NMR (83 MHz, $CHCl_3$) δ 2.94 (s, 1 D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 141.1, 138.8, 128.6, 128.5, 126.9, 126.8, 126.7, 82.4, 80.5, 43.3 (t, J_{CD} = 19.3 Hz), 38.4, 28.7, 28.5, 27.9, 16.3; IR (film) 1364 cm^{-1}. MS (ESI) *m/z* 304.1788 (304.1787 calcd for $C_{20}H_{23}DNaO$, M + Na^+).

Table 4. Selected NMR Data for the mixture of 32, 33, and 30

	 **32**		 **33**		 **30**		
	δ 4.16 (H_A/D_A)	2.94 (D_B/H_B)	4.07 (D_A/H_A)	2.80 (H_B/D_B)	3.94 (H_A/D_A)	3.12 (H_B/D_B)	1.65 (D_C/H_C)
^{1}H NMR Integral Area	100	5	6	26	7	8	ND
^{2}H NMR Integral Area	2	100	21	5	0	0	2

(*E*)-7,7,7-Trideuterio-2-methylhept-5-en-2-ol (34). A flame-dried flask was cooled under a stream of argon and charged with magnesium turnings (3.60 g, 150 mmol). The flask was purged with argon, diethyl ether (25 mL) was added, and the resulting suspension was cooled to 0 °C.

Trideuteriomethyl iodide (7.25 g, 50 mmol) was added dropwise and the resulting mixture was warmed to rt and stirred for 2 h. The resulting solution was transferred to a dry, argon filled flask via cannula and additional diethyl ether (20 mL) was added by syringe. A solution of acrolein (2.10 g, 37.6 mmol) in diethyl ether (10 mL) was cooled to 0 °C and added dropwise to the Grignard solution. The resulting mixture was stirred at rt for 8 h, and then saturated aqueous NH_4Cl (30 mL) was added dropwise. The reaction mixture was diluted with diethyl ether (40 mL) and the aqueous layer was removed and extracted with diethyl ether (2 x 20 mL). The organic layers were combined and dried over anhydrous Na_2SO_4, decanted, and concentrated by fractional distillation to afford 607 mg (21 %) of 1,1,1-trideuteriobut-3-en-2-ol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddd, J = 6.4, 10.4, 17.0 Hz, 1 H), 5.20 (d, J = 17.2 Hz, 1 H), 5.06 (d, J = 10.4 Hz, 1 H), 4.28 (d, J = 5.6 Hz, 1 H), 1.62 (s, 1 H).

1,1,1-Trideuteriobut-3-en-2-ol (607 mg, 8.1 mmol) was treated with triethylorthoacetate according to general procedure 2 to afford 600 mg (51 %) of (*E*)-6,6,6-trideuteriohex-4-enoic acid ethyl ester as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45–5.39 (m, 2 H), 4.12 (q, J = 7.0 Hz, 2 H), 2.36–2.32 (m, 2 H), 2.31–2.27 (m, 2 H), 1.24 (t, J = 7.0 Hz, 3 H).

(E)-6,6,6-trideuteriohex-4-enoic acid ethyl ester (600 mg, 4.1 mmol) was treated with MeMgBr (6.8 mL, 20.5 mmol, 3.0 M solution in diethyl ether) according to general procedure 1 to afford 325 mg (61 %) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45–5.44 (m, 2 H), 2.09–2.04 (m, 2 H), 1.54–1.51 (m, 2 H), 1.30 (s, 1 H), 1.21 (s, 6 H); ^{2}H NMR (83 MHz, $CHCl_3$) δ 1.58 (s, 3D); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.4, 124.7, 70.8, 43.3, 29.1, 27.5, 17.2 (m); IR (film) 3369 cm^{-1}; MS (EI) *m/z* 113.1285 (113.1281 calcd for $C_8H_{13}D_3O–H_2O$).

Palladium-Catalyzed Reaction of (*E*)-7,7,7-Trideuterio-2-methylhept-5-en-2-ol with 4-bromobiphenyl (eq 5). Reaction of 64.5 mg (0.5 mmol) of (*E*)-7,7,7-trideuterio-2-methylhept-5-en-2-

ol with 4-bromobiphenyl (233 mg, 1.0 mmol) according to the general procedure afforded 100 mg (70 %) of (±)-(1'*S*,5*R*)-5-[1'-(4-Phenyl)phenylethyl]-2,2-dimethyltetrahydrofuran-D-3 The material was isolated as a ca. 71:23:6 mixture of **35**:**36**:**37** as judged by ^{1}H NMR analysis; all isomers contained three deuterium atoms as judged by MS analysis. All three isomers were trideuterated at the C1' methyl group. Complete data are given for the major diastereomer **35**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.0 Hz, 2 H), 7.59 (d, *J* = 8.0 Hz, 2 H), 7.48 (t, *J* = 8.0 Hz, 2 H), 7.40–7.37 (m, 3 H), 4.17 (q, *J* = 6.0 Hz, 1 H), 2.92 (d, *J* = 5.5 Hz, 1 H), 1.90–1.84 (m, 1 H), 1.78–1.70 (m, 1 H), 1.67–1.51 (m, 2 H), 1.21 (s, 6 H); ^{2}H NMR (83 MHz, $CHCl_3$) δ 1.30 (s, 3 D) ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 141.1, 138.8, 128.6, 128.5, 126.9, 126.8, 126.7, 82.5, 80.5, 43.5, 38.4, 28.7, 28.5, 27.9, 16.3 (m); IR (film) 1364 cm^{-1}. MS (ESI) *m/z* 306.1913 (306.1910 calcd for $C_{20}H_{21}D_3NaO$, M + Na^+).

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