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Stereochemistry and Construction of Tetrasubstituted Chiral Carbon Centers in Intramolecular Pd-Catalyzed 1,3-Chirality Transfer Reactions

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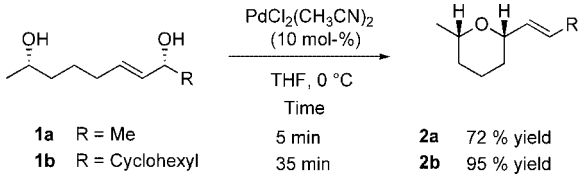
A Pd^{II}-catalyzed cyclization for the construction – from chiral allylic alcohols – of tetrahydropyrans containing tetrasubstituted chiral carbons proceeded stereospecifically by 1,3-chirality transfer through a *syn*-S_N2' type process. The chiral 2,2,6-trisubstituted tetrahydropyrans **5** and spiro hydropyrans **6** were obtained in high yields under mild reaction conditions.

Introduction

The construction of tetrasubstituted chiral carbon moieties is one of the most important issues in organic chemistry and their stereoselective formation is an important challenge for organic chemists.[1] Compounds containing tetrasubstituted chiral carbon systems in tetrahydropyran rings occur in the form of natural products such as kalihinol A,[2] venustatriol,[3] and thyrsiferol,[4] all exhibiting important biological activities. These units are found in both monocyclic and polycyclic structures, fused with carbocyclic or other cyclic ethers, or spiroketals. Fascination with their properties has resulted in the synthesis of such moieties having been developed through a wide range of methods,[5] including an alkylation of 2-cyano-tetrahydropyrans,[6] a Lewis acid-promoted alkylation of *exo*-glycals,[7] and an intramolecular addition of alcohols to olefins.[8]

Pd^{II}-promoted intramolecular ring formation is a powerful method for the construction of heterocycles.[9] We have developed a Pd^{II}-catalyzed cyclization for the stereoselective construction of substituted tetrahydropyrans by intramolecular S_N2'-type cyclization with 1,3-chirality transfer. This methodology has provided great advantages for the stereodifferentiated preparation of *cis*- and *trans*-2,6-disubstituted 3,6-dihydro-2*H*-pyrans from ζ-hydroxy-α,β,δ,ε-unsaturated alcohols and of 2,6-disubstituted tetrahydropyrans from ζ-hydroxy-α,β-unsaturated alcohols.[10]

As shown in Scheme 1, for example, the allylic alcohols **1a** (R = Me) and **1b** (R = cyclohexyl) cyclized to give the corresponding tetrahydropyrans **2a** and **2b**, with the newly generated chiral centers on the tetrahydropyran rings being transcripted stereospecifically. Namely, an (*R*)-*allylic alcohol* gave an (*S*) *chiral center*, while an (*S*)-*allylic alcohol* gave an (*R*) *chiral center* in the cyclization reactions. If an additional alkyl group is located at the β-position in the chiral allylic alcohol, the reaction provides 2,2,6-trisubstituted chiral tetrahydropyrans. The stereochemistry of the newly generated tetrasubstituted carbon center could be transferred from the stereochemistry of the original allylic alcohol, but the surrounding substituents around the allylic alcohol seemed to influence the reaction rate of the cyclization: the reaction of **1a** (R = Me), for example, was completed within 5 min, but that of **1b**, with a larger substituent (R = cyclohexyl), required 35 min. From our proposed reaction mechanism and the experimental results, we assumed that the rate-determining step might be the formation of a π-allyl Pd complex. We therefore became interested in the cyclization reaction for highly substituted allylic alcohols such as **3a**, **3b**, **4a**, and **4b** and the potential for the synthesis of the 2,2,6-trisubstituted chiral tetrahydropyrans **5a** and **5b** as well as spiro pyrans **6a** and **6b** (Figure 1). Here we describe the cyclization reactions and their results.



Scheme 1.

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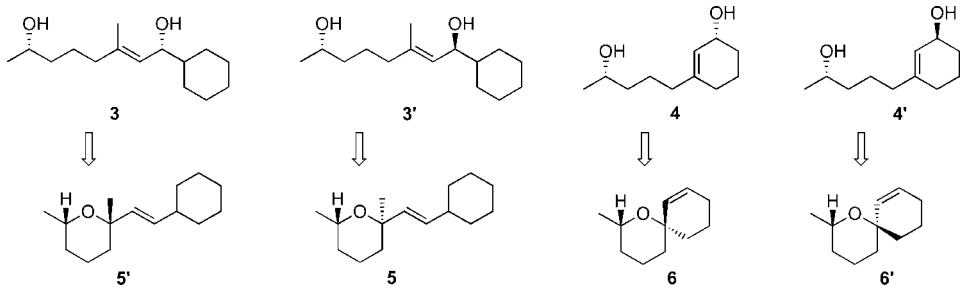


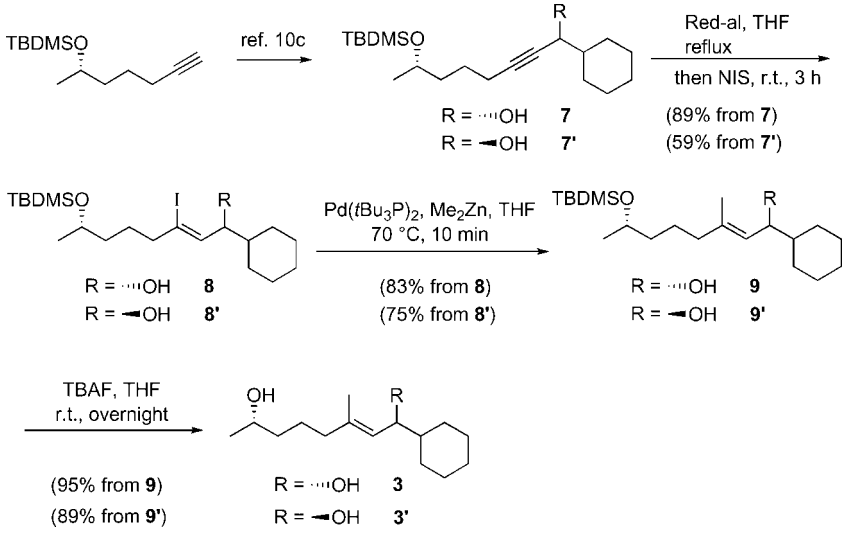
Figure 1. Structures of the cyclized products and their acyclic precursors.

Results and Discussion

Four optically pure diols – **3**, **3′**, **4**, and **4′** – each possessing a trisubstituted (*E*)-allylic alcohol or a cyclohexenol with an (*R*) or (*S*) chiral center, were chosen as precursors for the cyclization. When diols **3** and **3′** are cyclized, four kinds of tetrahydropyrans – **5′**, **5**, and the corresponding (*Z*) isomers – are formed. In the case of cyclization of **4** and **4′**, the spiro tetrahydropyrans **6′** and **6** are formed (Figure 1).

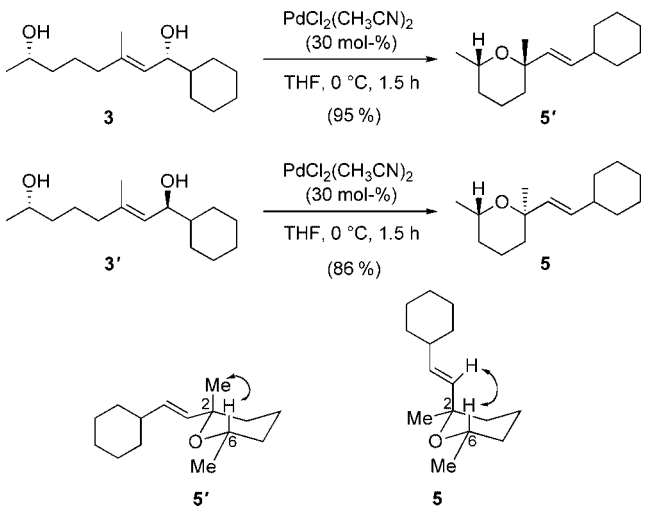
In our previous report,[10c] asymmetric alkynylation was used for stereoselective preparations of allylic alcohol **7** with utilization of Carreira's conditions.[11] The excellent diastereoselectivities (99% *de*) observed in the asymmetric reaction encouraged us to synthesize β,β-disubstituted allylic alcohol moieties from adducts **7′** [12] and **7**.[13] The partial reduction of the triple bonds in **7** and **7′** with Red-al, followed by treatment with NIS, afforded the vinyl iodides **8** and **8′** in 89% and 59% yields,[13] respectively, as shown in Scheme 2. The vinyl iodides **8** were suitable intermediates for introduction of carbon substituents – alkyl or alkenyl or alkynyl groups – through cross-coupling reactions.[14] Indeed, cross-coupling of **8** and **8′** with Me_2Zn and catalytic $Pd(tBu_3P)_2$ in THF proceeded very smoothly to afford the trisubstituted alkenes **9** and **9′** in 83% and 75% yields,[13] respectively. The use of $NiCl_2$(dppf) as a catalyst gave **9** in a lower yield, accompanied by significant amounts of the dimer. Deprotection of the silyl ethers **9** and **9′** with TBAF afforded the diols **3** and **3′** in 95% and 89% yields,[13] respectively.

With the diols **3** and **3′** to hand, Pd^{II}-catalyzed cyclizations were examined as shown in Scheme 3. The diol **3** was not completely consumed in the formation of the pyran ring when it was treated at 0 °C with $PdCl_2(CH_3CN)_2$ (10 mol-%) in THF for several hours, under the same conditions as in our previous report,[10c] but when the amount of catalyst was increased to 30 mol-%, the *cis*-(*E*)-tetrahydropyran **5′** was obtained as a single isomer in 95% yield after 1.5 h. Meanwhile, under the same conditions, the diol **3′** was completely consumed after 1.5 h and gave the desired *trans*-(*E*)-tetrahydropyran **5** in 92% yield. The configurations of **5′** and **5** were established by nOe experiments. For compound **5′**, a nOe between 2-CH_3 and 6-*H* indicated that 2-CH_3 and 6-*H* were in the same orientation on the tetrahydropyran ring. On the other hand, for compound **5**, the 6-*H* displayed a nOe to the vinyl proton while no nOe between 2-CH_3 and



Scheme 2. Preparation of compounds **3** and **3′**.

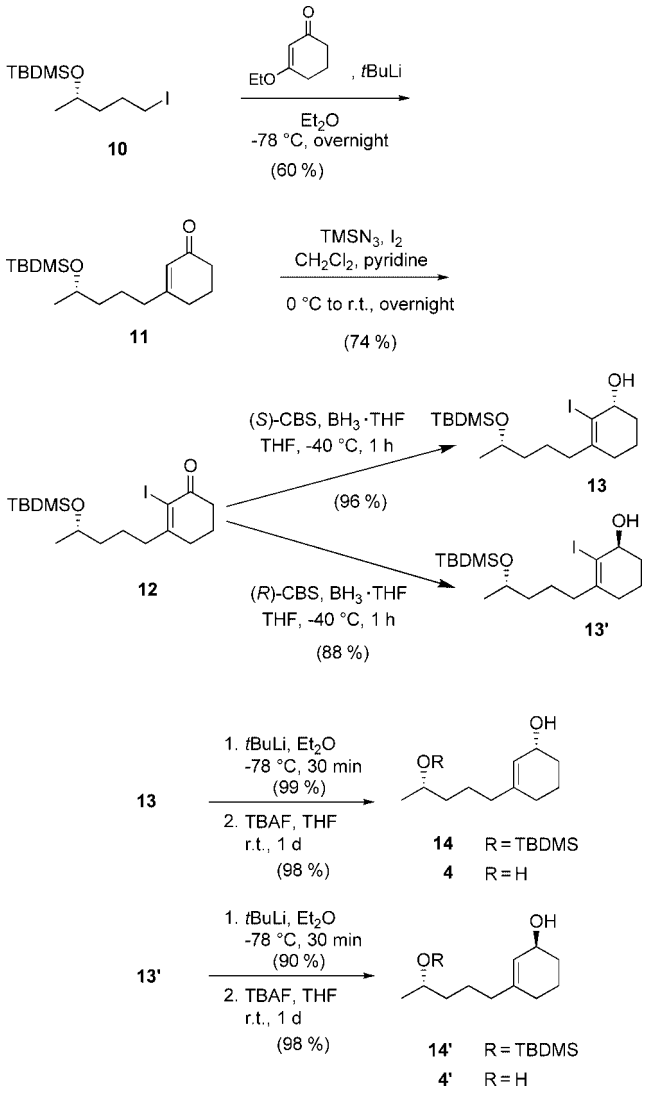
6-CH_3 was observed, which indicates a *trans* orientation on the tetrahydropyran ring and that the C2-alkenyl group is located in an axial position.



Scheme 3. Cyclizations of **3** and **3′**.

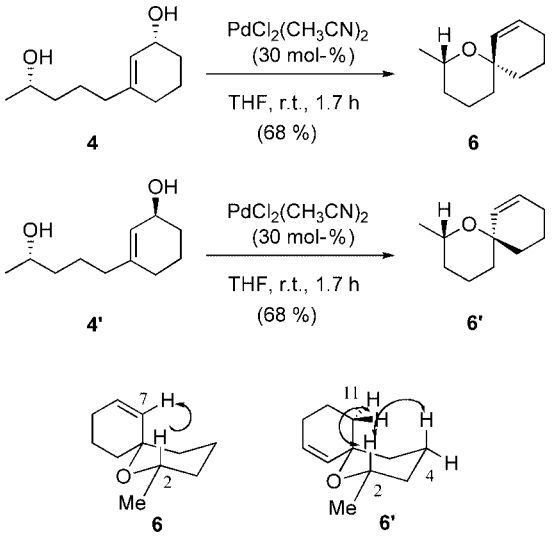
For the preparation of **4** and **4′** for construction of the spiro pyran rings, we began by synthesizing the α,β-unsaturated cyclohexenone **11**, as shown in Scheme 4. Alkylation of β-ethoxycyclohexenone with the alkyllithium generated from the known iodide **10**[15] by halogen/metal exchange followed by acid treatment afforded the unsaturated ketone **11** in 60% yield. The stereoselective reduction of C2-substituted cyclohexenones has been reported to proceed with high stereoselectively to afford the allylic alcohols. On the other hand, a C2-unsubstituted cyclohexenone has been found to be unsuitable for the stereoselective CBS reduction.[16] Indeed, a CBS reduction of **11** and a lipase-catalyzed kinetic acetylation of the cyclohexenol gave poor selectivities.[17] We therefore chose to introduce iodide at the α-position of **11** as an auxiliary, to reduce the carbonyl group of the iodo unsaturated ketone by use of a CBS reagent, and then to remove the iodide from the alcohols produced.[18] Treatment of **11** with I_2 and $TMSN_3$ in the presence of pyridine afforded vinyl iodide **12** in 74% yield,[16] while Corey's reduction of **12** proceeded very smoothly with an (*S*)-CBS reagent and BH_3·THF complex as a reductant to afford the *syn* alcohol **13** in 96% yield and with 99% *de*.[13] Meanwhile, by treatment with (*R*)-CBS reagent, **13′** was obtained in 88% yield and with 99% *de*.[19] Finally, removal of the iodide in **13** and **13′** with *t*BuLi in Et_2O at –78 °C, followed by desilylation with TBAF, afforded the desired diols **4** and **4′** in 94% and 88% yields,[13] respectively.

With the diols **4** and **4′** to hand, Pd^{II}-catalyzed cyclizations were examined as shown in Scheme 5. When diol **4** was treated with $PdCl_2(CH_3CN)_2$ (30 mol-%) in THF the cyclization reaction proceeded poorly at 0 °C even with prolongation of the reaction time. At room temperature, in contrast, the starting material was completely consumed after 1.7 h and the desired spiro tetrahydropyran **6** was obtained as a single isomer. Meanwhile, under the same conditions, diol **4′** was also completely consumed after 1.7 h to afford the desired spiro tetrahydropyran **6′** in 68% yield. Although both reactions proceeded very smoothly in THF at room temperature, as judged both by the ^{1}H NMR spectra of the crude mixtures as well as by TLC analysis, the chemical yields of **6** and **6′** after isolation appeared to be less than the actual yields, due to their volatile characters. The configurations of **6** and **6′** were determined by nOe experiments. In compound **6**, a nOe between 7-*H* and 2-*H* indicated that the alkenyl moiety on the cyclohexene ring and 2-*H* had the same orientation on the tetrahydropyran ring. On the other hand, in compound **6′**, an nOe was observed between 2-*H* and 11-*H* and 4-*H*, which confirmed the structure of **6′**.



Scheme 4. Preparation of compounds **4** and **4′**.

Comparison of reaction temperatures and times for the formation of **5** and of **6** shows that the cyclizations of **4** were harder than those of **3**, which might be more strongly influenced by steric factors.



Scheme 5. Cyclizations of **4** and **4′**.

Conclusions

We have described the high efficiency and utility of the Pd^{II}-catalyzed cyclization of chiral β-substituted ζ-hydroxy-α,β-unsaturated alcohols **3** and **4** for the synthesis of the 2,2,6-trisubstituted chiral tetrahydropyrans **5** and **5′** as well as the spiro pyrans **6** and **6′**. Although 30 mol-% of Pd catalyst are required for the reaction, the chirality has been transferred with perfect stereospecificity from the chiral allylic alcohol to a newly generated tetrasubstituted carbon center. This methodology should be valuable for the synthesis of biologically important natural products and medicinal compounds containing highly substituted chiral tetrahydropyran units.

Experimental Section

General: Ether, THF, and toluene were distilled from sodium and benzophenone. CH_2Cl_2 was distilled from P_2O_5. All other reagents were used without further purification. Unless otherwise stated, all reactions were run under argon. ^1H and ^{13}C NMR spectra were obtained at 25 °C with a JEOL JNM-AL-300 (300 MHz and 75 MHz) instrument and 2D NMR experiments were recorded on Varian 400 MHz spectrometer. Proton chemical shifts were internally referenced to the residual proton resonance in $CDCl_3$ (δ = 7.26 ppm). Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (δ = 77.00 ppm). Mass spectra were recorded on a JEOL-GC instrument, IR spectra were recorded on a JASCO FT/IR-410, and optical rotations were recorded on a JASCO DIP-360. Chiral HPLC analyses were performed on a SHIMADZU SPD-6A instrument. TLC was run on Merck $60F_{254}$ plates.

(1*R*,7*S*)- and (1*S*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-1-cyclohexyl-3-iodooct-2-en-1-ol (8 and 8′): Red-al (3.6 M in hexane, 66 mL, 0.24 mmol, 2 equiv.) was added at 0 °C to a solution of **7**[10c] (40 mg, 0.12 mmol) in THF (4 mL). The reaction mixture was heated at reflux for 2 h and a solution of NIS (58.8 mg, 0.26 mmol, 2.2 equiv.) in THF (4 mL) was then added. After removal of the oil bath, the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched by the addition of saturated NH_4Cl solution (1 mL) and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine (1 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by SiO_2 column chromatography (CH_2Cl_2) gave the vinyl iodide **8** (49.8 mg, 89%). By the same procedure, **8′** was obtained from **7′** in 59% yield (33 mg).

Compound 8: Pale yellow oil; R_f = 0.50 (CH_2Cl_2). $[\alpha]_D^{22}$ = +16.0 (*c* = 0.63, $CHCl_3$). ^1H NMR: δ = 0.07 (s, 6 H, CH_3Si), 0.90 [s, 9 H, C(CH_3)$_3$], 0.97–1.75 (m, 15 H), 1.13 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.91–1.95 (m, 1 H), 2.51 (m, 2 H), 3.80 (m, 1 H, C*H*OH), 4.08 (m, 1 H, C*H*OH), 5.57 (d, *J* = 8.1 Hz, 1 H, C*H*=CI) ppm. ^{13}C NMR: δ = –4.7, –4.3, 18.1, 23.8, 25.4, 25.9, 26.1, 26.5, 28.6, 28.7, 38.2, 43.4, 45.6, 68.3, 80.5, 111.4, 135.9 ppm. IR: $\tilde{\nu}$ = 3366, 2926, 2854, 1643, 1449, 1374, 1253, 1136, 1094, 1006, 892, 835, 807, 774 cm^{-1}. MS (FAB): *m*/*z* (%) = 489 (6.3) $[M + Na]^+$, 73 (100). HRMS (FAB): $C_{20}H_{39}INaO_2Si$ calcd. 489.1662; found 489.1658.

Compound 8′: Pale yellow oil; R_f = 0.50 (CH_2Cl_2). $[\alpha]_D^{22}$ = –1.57 (*c* = 1.40, $CHCl_3$). ^1H NMR: δ = 0.05 (s, 6 H, CH_3Si), 0.89 [s, 9 H, C(CH_3)$_3$], 0.99–1.74 (m, 15 H), 1.12 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.89–1.94 (m, 1 H), 2.49 (m, 2 H), 3.78 (m, 1 H, C*H*OH), 4.06 (m, 1 H, C*H*OH), 5.55 (d, *J* = 8.0 Hz, 1 H, C*H*=CI) ppm. ^{13}C NMR: δ = –4.7, –4.3, 18.1, 23.8, 25.5, 25.9, 26.1, 26.5, 28.6, 28.6, 38.1, 43.4, 45.5, 68.3, 80.5, 111.4, 136.0 ppm. IR: $\tilde{\nu}$ = 3367, 2926, 2854, 1942, 1449, 1374, 1253, 1136, 1094, 1006, 892, 835, 807, 774 cm^{-1}. MS (FAB): *m*/*z* (%) = 489 (35.2) $[M + Na]^+$, 73 (100). HRMS (FAB): $C_{20}H_{39}INaO_2Si$ calcd. 489.1662; found 489.1656.

(2*E*,1*R*,7*S*)- and (2*E*,1*S*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-1-cyclohexyl-3-methyloct-2-en-1-ol (9 and 9′): $Pd(tBu_3P)_2$ (2.1 mg, 4.3 mmol, 0.05 equiv.) and dimethylzinc (1 M in hexane, 0.17 mL, 0.17 mmol, 2 equiv.) were added at 0 °C to a solution of vinyl iodide **8** (39.8 mg, 85.3 μmol) in THF (0.8 mL). The reaction mixture was stirred at 70 °C for 10 min. After quenching of the reaction by the addition of saturated NH_4Cl solution (1 mL), the aqueous layer was extracted with hexane (3 × 5 mL). The combined organic layers were washed with brine (1 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by SiO_2 column chromatography (CH_2Cl_2) gave **9** (25.1 mg, 83%). By the same procedure, **9′** was obtained from **8′** in 75% yield (22.6 mg).

Compound 9: Colorless oil. R_f = 0.33 (hexane/EtOAc, 4:1). $[\alpha]_D^{20}$ = +8.2 (*c* = 0.74, $CHCl_3$). ^1H NMR: δ = 0.05 (s, 6 H, CH_3Si), 0.88 [s, 9 H, C(CH_3)$_3$], 0.91–1.52 (m, 10 H), 1.11 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.65 (d, *J* = 1.1 Hz, 3 H, CH_3), 1.65–1.89 (m, 4 H), 1.94–2.02 (m, 3 H), 3.78 (m, 1 H, C*H*OH), 4.07 (dd, *J* = 8.9, 7.2 Hz, 1 H, C*H*OH), 5.17 (dd, *J* = 8.9, 1.1 Hz, 1 H, C*H*=C) ppm. ^{13}C NMR: δ = –4.7, –4.4, 16.6, 18.1, 23.8, 23.8, 25.9, 25.9, 26.0, 26.1, 26.6, 28.5, 28.9, 39.2, 39.7, 44.3, 68.5, 72.8, 72.9, 126.4, 139.2 ppm. IR: $\tilde{\nu}$ = 3360, 2927, 1449, 1374, 1254, 1137, 1005, 836, 774 cm^{-1}. MS (FAB): *m*/*z* (%) = 377 (19.1) $[M + Na]^+$, 73 (100). HRMS (FAB): $C_{21}H_{42}NaO_2Si$ calcd. 377.2852; found 377.2848.

Compound 9′: Colorless oil. R_f = 0.33 (hexane/EtOAc, 4:1). $[\alpha]_D^{20}$ = +6.4 (*c* = 0.64, $CHCl_3$). ^1H NMR: δ = 0.04 (s, 6 H, CH_3Si), 0.88 [s, 9 H, C(CH_3)$_3$], 1.03–1.50 (m, 10 H), 1.11 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.65 (d, *J* = 1.3 Hz, 3 H, CH_3), 1.64–1.73 (m, 4 H), 1.89–2.02 (m, 3 H), 3.78 (m, 1 H, C*H*OH), 4.07 (dd, *J* = 9.0, 7.2 Hz, 1 H, C*H*OH), 5.17 (dd, *J* = 9.0, 1.3 Hz, 1 H, C*H*=C) ppm. ^{13}C NMR: δ = –4.7, –4.4, 16.6, 18.1, 23.9, 23.9, 25.9, 26.0, 26.1, 26.6, 28.5, 29.0, 39.2, 39.7, 44.3, 68.4, 72.9, 126.5, 139.2 ppm. IR: $\tilde{\nu}$ = 3367, 2927, 2855, 1669, 1449, 1374, 1254, 1137, 1006, 892, 835, 806, 774 cm^{-1}. MS (FAB): *m*/*z* (%) = 377 (11.3) $[M + Na]^+$, 73 (100). HRMS (FAB): $C_{21}H_{42}NaO_2Si$ calcd. 377.2852; found 377.2843.

General Method for Preparation of Diols

(1*R*,7*S*)- and (1*S*,7*S*)-1-Cyclohexyl-3-methyloct-2-ene-1,7-diol (3 and 3′) and (1*S*,4′*S*)- and (1*R*,4′*S*)-3-(4′-Hydroxypentyl)cyclohex-2-enol (4 and 4′): TBAF (1 M in hexane, 0.55 mL, 0.55 mmol, 4.6 equiv.) was added at room temperature to a solution of monosilylated diol (0.12 mmol) in THF (0.4 mL). The reaction mixture was stirred at room temperature overnight or for 1 d. After the addition of saturated NH_4Cl solution (1 mL), the aqueous layer was extracted with diethyl ether (3 × 5 mL) and the combined organic layers were washed with brine (1 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by SiO_2 column chromatography (CH_2Cl_2) gave the diol.

Compound 3: This compound was obtained from **9** in 95% yield (27.3 mg). Colorless oil. R_f = 0.57 (Et_2O). $[\alpha]_D^{21}$ +4.3 (*c* = 0.73, $CHCl_3$). ^1H NMR: δ = 0.88–1.25 (m, 5 H), 1.19 (d, *J* = 6.2 Hz, 3 H, C*H*$_3$), 1.28–1.60 (m, 9 H), 1.61–1.78 (m, 3 H), 1.66 (d, *J* = 1.3 Hz, 3 H, C*H*$_3$), 1.89–2.05 (m, 2 H), 3.80 (m, 1 H, C*H*OH), 4.07 (dd, *J* = 8.9, 7.2 Hz, 1 H, C*H*OH), 5.18 (dq, *J* = 8.9, 1.3 Hz, 1 H, C*H*=C) ppm. ^{13}C NMR: δ = 16.6, 23.6, 23.9, 26.0, 26.1, 26.6, 28.6, 28.9, 38.9, 39.6, 44.3, 68.0, 72.9, 126.6, 138.9 ppm. IR: $\tilde{\nu}$ = 3348, 2922, 2852, 1668, 1449, 1374, 1174, 1129, 1083, 1004, 892, 733 cm^{-1}. MS (FAB): *m*/*z* (%) = 263 (100) $[M + Na]^+$. HRMS (FAB): $C_{15}H_{28}NaO_2$ calcd. 263.1987; found 263.1984.

Compound 3′: This compound was obtained from **9′** in 89% yield (25.6 mg). Colorless oil. R_f = 0.57 (Et_2O). $[\alpha]_D^{21}$ +5.7 (*c* = 0.40, $CHCl_3$). ^1H NMR: δ = 0.85–1.25 (m, 5 H), 1.19 (d, *J* = 6.2 Hz, 3 H, C*H*$_3$), 1.29–1.58 (m, 9 H), 1.62–1.77 (m, 3 H), 1.66 (d, *J* = 1.1 Hz, 3 H, C*H*$_3$), 1.89–2.07 (m, 2 H), 3.78 (m, 1 H, C*H*OH), 4.07 (dd, *J* = 8.8, 7.2 Hz, 1 H, C*H*OH), 5.17 (dq, *J* = 8.8, 1.5 Hz, 1 H, C*H*=C) ppm. ^{13}C NMR: δ = 16.6, 23.6, 23.8, 26.0, 26.1, 26.6, 28.6, 28.9, 38.8, 39.6, 44.3, 68.0, 72.9, 126.6, 138.9 ppm. IR: $\tilde{\nu}$ = 3365, 2924, 2852, 1667, 1449, 1375, 1261, 1172, 1128, 1082, 1003, 891 cm^{-1}. MS (FAB): *m*/*z* (%) = 263 (20.8) $[M + Na]^+$, 57 (100). HRMS (FAB): $C_{15}H_{28}NaO_2$ calcd. 263.1987; found 263.1993.

Compound 4: This compound was obtained from **14** in 98% yield (21.6 mg). Colorless oil. R_f = 0.46 (Et_2O). $[\alpha]_D^{22}$ +37.5 (*c* = 0.32, $CHCl_3$). ^1H NMR: δ = 1.19 (d, *J* = 6.1 Hz, 3 H), 1.38–1.61 (m, 8 H), 1.63–1.87 (m, 2 H), 1.92–2.09 (m, 4 H), 3.80 (m, 1 H, C*H*OH), 4.19 (m, 1 H, C*H*OH), 5.51 (m, 1 H, C*H*=C) ppm. ^{13}C NMR: δ = 19.1, 23.5, 23.6, 28.4, 31.9, 37.4, 38.8, 65.9, 67.9, 123.9, 142.1 ppm. IR: $\tilde{\nu}$ = 3350, 2929, 1667, 1456, 1373, 1288, 1128, 1071, 1023, 961, 909, 876, 828 cm^{-1}. MS (FAB): *m*/*z* (%) = 207 (9.3) $[M + Na]^+$, 57 (100). HRMS (FAB): $C_{11}H_{20}NaO_2$ calcd. 207.1361; found 207.1353.

Compound 4′: This compound was obtained from **14′** in 98% yield (21.6 mg). Colorless oil. R_f = 0.46 (Et_2O). $[\alpha]_D^{24}$ –33.2 (*c* = 0.65, $CHCl_3$). ^1H NMR: δ = 1.19 (d, *J* = 6.2 Hz, 3 H, C*H*$_3$), 1.40–1.60 (m, 8 H), 1.71–1.85 (m, 2 H), 1.92–2.02 (m, 4 H), 3.80 (m, 1 H, C*H*OH), 4.20 (m, 1 H, C*H*OH), 5.51 (m, 1 H, C*H*=C) ppm. ^{13}C NMR: δ = 19.1, 23.5, 23.6, 28.4, 31.9, 37.4, 38.9, 65.9, 68.0, 123.9, 142.2 ppm. IR: $\tilde{\nu}$ = 3349, 2927, 1666, 1454, 1372, 1129, 1021, 960, 909, 879, 838 cm^{-1}. MS (FAB): *m*/*z* (%) = 207 (13.1) $[M + Na]^+$, 57 (100). HRMS (FAB): $C_{11}H_{20}NaO_2$ calcd. 207.1361; found 207.1353.

(2*S*)-2-(*tert*-Butyldimethylsilyloxy)-5-iodopentane (10):[15] $NaBH_4$ (275.8 mg, 7.29 mmol, 1.5 equiv.) was added at 0 °C to a solution of aldehyde[15] (1.05 g, 4.86 mmol) in methanol (30 mL) and the reaction mixture was stirred at room temperature for 1 h. After addition of water (30 mL), the aqueous layer was extracted with ethyl acetate (3 × 70 mL), and the combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (hexane/EtOAc, 3:1) gave the alcohol as a colorless oil (963.9 mg, 91%).

Imidazole (660.5 mg, 9.7 mmol, 2.2 equiv.) and triphenylphosphane (1.272 g, 4.85 mmol, 1.1 equiv.) were added to a solution of the alcohol (963.9 mg, 4.41 mmol) in THF (45 mL). The reaction mixture was stirred at room temperature for 5 min and then cooled to 0 °C before addition of iodine (1.23 g, 4.85 mmol, 1.1 equiv.). The reaction mixture was stirred for 0.5 h at room temperature, and after dilution with hexane (45 mL) the mixture was filtered and concentrated in vacuo. Purification of the residue by SiO_2 column chromatography (hexane) gave the iodide **10**[15] (1.28 g, 88%): pale colorless oil.

(4′*S*)-3-[4′-(*tert*-Butyldimethylsilyloxy)pentyl]cyclohex-2-enone (11): *t*BuLi (1.59 M in pentane, 0.69 mL, 1.1 mmol, 1.6 equiv.) was added at –78 °C to a solution of **10** (200 mg, 0.61 mmol) in diethyl ether (4 mL). The reaction mixture was stirred for 4 h and a solution of ethoxycyclohexenone (76.9 mg, 0.55 mmol, 0.9 equiv.) in diethyl ether (1 mL) was added. The mixture was stirred overnight at –78 °C and was then quenched by the addition of saturated NH_4Cl solution (2 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with a saturated NH_4Cl solution (2 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by SiO_2 column chromatography (hexane/Et_2O, 1:1) provided the coupling product **11** (97.7 mg, 60%). Colorless oil. R_f = 0.51 (hexane/EtOAc, 1:1). $[\alpha]_D^{23}$ = +12.8 (*c* = 0.54, $CHCl_3$). ^1H NMR: δ = 0.04 (s, 3 H, C*H*$_3$Si), 0.05 (s, 3 H, C*H*$_3$Si), 0.88 (s, 9 H, C*H*$_3$CSi), 1.11 (d, *J* = 6.1 Hz, 3 H, C*H*$_3$), 1.33–1.68 (m, 4 H), 1.98 (m, 2 H), 2.21 (m, 2 H), 2.27 (bt, *J* = 5.7 Hz, 2 H), 2.36 (dd, *J* = 7.2, 6.2 Hz, 2 H), 3.79 (m, 1 H, C*H*OH), 5.17 (t, *J* = 1.3 Hz, 1 H, C*H*=C) ppm. ^{13}C NMR: δ = –4.7, –4.3, 18.1, 22.7, 22.9, 23.8, 25.8, 29.6, 37.4, 39.1, 39.1, 68.2, 125.7, 166.4, 199.9 ppm. IR: $\tilde{\nu}$ = 2929, 1673, 1626, 1462, 1373, 1253, 1191, 1133, 1088, 1026, 889, 836, 774 cm^{-1}. MS (FAB): *m*/*z* (%) = 297 (41.9) $[M + H]^+$, 239 (100). HRMS (FAB): $C_{17}H_{33}O_2Si$ calcd. 297.2250; found 297.2245.

(4′*S*)-3-[4′-(*tert*-Butyldimethylsilyloxy)pentyl]-2-iodocyclohex-2-enone (12): $TMSN_3$ (86.3 mL, 0.66 mmol, 2.0 equiv.) was added at 0 °C to a solution of hexenone **11** (97.7 mg, 0.33 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at 0 °C for 2 h and a solution of iodine (334.6 mg, 1.32 mmol, 4 equiv.) and pyridine (0.5 mL) in CH_2Cl_2 (0.5 mL) was added. The reaction mixture was allowed to warm slowly to room temperature and stirred overnight. After the addition of a saturated solution of $Na_2S_2O_3$ (1 mL), the aqueous layer was extracted with diethyl ether (3 × 5 mL) and the combined organic layers were washed with brine (1 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by SiO_2 column chromatography (hexane/Et_2O, 1:1) gave the vinyl iodide **12** (103.4 mg, 74%) as a pale yellow oil. R_f = 0.65 (hexane/EtOAc, 1:1). $[\alpha]_D^{22}$ +6.95 (*c* = 0.92, $CHCl_3$). ^1H NMR δ = 0.05 (s, 3 H, C*H*$_3$Si), 0.06 (s, 3 H, C*H*$_3$Si), 0.89 [s, 9 H, (C*H*$_3$)$_3$C], 1.14 (d, *J* = 6.1 Hz, 3 H, C*H*$_3$), 1.43–1.65 (m, 4 H), 1.94–2.01 (m, 2 H), 2.50–2.63 (m, 6 H), 3.82 (m, 1 H, C*H*OH) ppm. ^{13}C NMR: δ = –4.7, –4.3, 18.1, 22.3, 23.1, 23.7, 25.9, 32.5, 36.6, 39.3, 44.8, 68.1, 107.0, 169.9, 192.3 ppm. IR: $\tilde{\nu}$ = 2928, 2856, 1679, 1585, 1461, 1427, 1374, 1254, 1176, 1133, 1088, 1024, 975, 914, 835, 807, 774, 733 cm^{-1}. MS (FAB): *m*/*z* = 423 (11.7) $[M + H]^+$, 73 (100). HRMS (FAB): $C_{17}H_{32}IO_2Si$ calcd. 423.1216; found 423.1211.

(1*R*,4′*S*)- and (1*S*,4′*S*)-3-[4′-(*tert*-Butyldimethylsilyloxy)pentyl]-2-iodocyclohex-2-en-1-ol (13 and 13′): A mixed solution of (*R*)-CBS (1 M in toluene, 0.27 mL, 0.27 mmol, 1.2 equiv.) or (*S*)-CBS (1 M in toluene, 0.27 mL, 0.27 mmol, 1.2 equiv.) and BH_3·THF (1 M in

toluene, 0.27 mL, 0.27 mmol, 1.2 equiv.) in THF (0.7 mL) was stirred at room temperature for 30 min. The mixture was cooled to –40 °C, a solution of **12** (0.223 mmol, 1 equiv.) in THF (0.7 mL) was added, and the mixture was stirred for 1 h and quenched by the addition of methanol (2 mL). Concentration and purification by SiO_2 column chromatography (hexane/Et_2O, 1:1) gave the alcohols **13** or **13′**. The enantiomeric purity was determined by chiral HPLC after derivation of the corresponding benzoate (DAICEL CHIRALCEL AD-H). Eluent, hexane/propan-2-ol (99:1), flow rate: 0.1 mL min^{-1}, detection: 254 nm, retention time: 12.7 min (**13** (*R*) isomer), 19.1 min (**13′** (*S*) isomer).

Compound 13: This compound was obtained from **12** in 96% yield (90 mg). Colorless oil. $[\alpha]_D^{22}$ = +44.9 (*c* = 0.43, $CHCl_3$) (>99% *de*). R_f = 0.72 (hexane/Et_2O, 1:1). ^{1}H NMR: δ = 0.05 (s, 6 H, C*H*$_3$Si), 0.89 (s, 9 H, C*H*$_3$CSi), 1.13 (d, *J* = 6.1 Hz, 3 H, C*H*$_3$), 1.38–1.74 (m, 7 H), 1.75–1.92 (m, 2 H), 2.07–2.27 (m, 4 H), 3.81 (m, 1 H, C*H*OH), 4.29 (m, 1 H, C*H*OH) ppm. ^{13}C NMR: δ = –4.6, –4.4, 18.1, 18.6, 23.2, 23.7, 25.9, 31.5, 31.9, 39.2, 42.8, 68.3, 74.1, 104.6, 146.3 ppm. IR: $\tilde{\nu}$ = 3397, 2928, 1631, 1461, 1375, 1253, 1134, 1077, 903, 835, 774, 664 cm^{-1}. MS (FAB): *m*/*z* (%) = 447 (20.4) [M + Na]$^+$, 73 (100). HRMS (FAB): $C_{17}H_{33}INaO_2Si$ calcd. 447.1193; found 447.1201.

Compound 13′: This compound was obtained from **12** in 88% yield (83 mg). Colorless oil. $[\alpha]_D^{22}$ = –35.4 (*c* = 0.68, $CHCl_3$) (>99% *de*). R_f = 0.72 (hexane/Et_2O, 1:1). ^{1}H NMR: δ = 0.05 (s, 6 H, C*H*$_3$Si), 0.89 [s, 9 H, (C*H*$_3$)$_3$C], 1.13 (d, *J* = 6.1 Hz, 3 H, C*H*$_3$), 1.38–1.69 (m, 7 H), 1.78–1.91 (m, 2 H), 2.07–2.27 (m, 4 H), 3.80 (m, 1 H, C*H*OH), 4.29 (m, 1 H, C*H*OH) ppm. ^{13}C NMR: δ = –4.6, –4.4, 18.1, 18.6, 23.2, 23.7, 25.9, 31.5, 31.9, 39.2, 42.8, 68.3, 74.1, 104.6, 146.3 ppm. IR: $\tilde{\nu}$ = 3407, 2928, 2856, 1631, 1461, 1375, 1253, 1215, 1134, 1077, 1025, 960, 836, 759, 665 cm^{-1}. MS (FAB): *m*/*z* (%) = 447 (21.8) [M + Na]$^+$, 73 (100). HRMS (FAB): $C_{17}H_{33}INaO_2Si$ calcd. 447.1193; found 447.1199.

(1*R*,4′*S*)- and (1*S*,4′*S*)-3-[4′-(*tert*-Butyldimethylsilyloxy)pentyl]cyclohex-2-en-1-ol (14 and 14′): A solution of **13** (0.31 mmol) in Et_2O (4.5 mL) was treated at –78 °C with *t*BuLi (1.57 M in pentane, 0.70 mL, 1.1 mmol, 3.5 equiv.) and the reaction mixture was stirred for 30 min. After the addition of water (4 mL), the aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organic layers were washed with brine (1 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by SiO_2 column chromatography (hexane/Et_2O, 1:1) gave the desired compound **14**.

Compound 14: This compound was obtained from **13** in 99% yield (91 mg). Colorless oil. $[\alpha]_D^{24}$ = +36.8 (*c* = 1.07, $CHCl_3$). R_f = 0.44 (hexane/EtOAc, 1:1). ^{1}H NMR: δ = 0.05 (s, 6 H, C*H*$_3$Si), 0.89 (s, 9 H, C*H*$_3$CSi), 1.11 (d, *J* = 6.1 Hz, 3 H, C*H*$_3$), 1.33–1.43 (m, 4 H), 1.56–1.61 (m, 3 H), 1.72–1.81 (m, 2 H), 1.88–1.99 (m, 4 H), 3.78 (m, 1 H, C*H*OH), 4.19 (br s, 1 H, C*H*OH), 5.49 (m, 1 H, CH=C) ppm. ^{13}C NMR: δ = –4.7, –4.4, 18.1, 19.1, 23.5, 23.8, 25.9, 28.4, 31.9, 37.6, 39.3, 65.9, 68.5, 123.7, 142.4 ppm. IR: $\tilde{\nu}$ = 3339, 2930, 1665, 1462, 1373, 1254, 1135, 1087, 1030, 906, 835, 774 cm^{-1}. MS (FAB): *m*/*z* (%) = 321 (35.9) [M + Na]$^+$, 107 (100). HRMS (FAB): $C_{17}H_{34}NaO_2Si$ calcd. 321.2226; found 321.2220.

Compound 14′: This compound was obtained from **13′** in 90% yield (83 mg). Colorless oil. $[\alpha]_D^{22}$ = –18.2 (*c* = 0.96, $CHCl_3$). R_f = 0.44 (hexane/EtOAc, 1:1). ^{1}H NMR: δ = 0.05 (s, 6 H, C*H*$_3$Si), 0.89 (s, 9 H, C*H*$_3$CSi), 1.11 (d, *J* = 6.1 Hz, 3 H, C*H*$_3$), 1.32–1.43 (m, 4 H), 1.56–1.61 (m, 3 H), 1.72–1.81 (m, 2 H), 1.89–1.98 (m, 4 H), 3.78 (m, 1 H, C*H*OH), 4.19 (br s, 1 H, C*H*OH), 5.49 (m, 1 H, C*H*=C) ppm. ^{13}C NMR: δ = –4.7, –4.4, 18.1, 19.1, 23.5, 23.8, 25.9, 28.4, 31.9, 37.6, 39.3, 65.9, 68.5, 123.7, 142.5 ppm. IR: $\tilde{\nu}$ = 3336, 2929, 1665, 1462, 1373, 1253, 1135, 1029, 905, 835, 773, 700 cm^{-1}. MS (FAB): *m*/*z* (%) = 321 (30.9) [M + Na]$^+$, 107 (100). HRMS (FAB): $C_{17}H_{34}NaO_2Si$ calcd. 321.2226; found 321.2219.

General Method for Palladium-Catalyzed Cyclization (5′, 5, 6′, and 6): A solution of diol **3** or **4** (58.6 μmol) in THF (0.6 mL) was added at 0 °C or room temperature to a solution of $PdCl_2(CH_3CN)_2$ (4.6 mg, 17.6 μmol, 0.3 equiv.) in THF (0.6 mL). The reaction mixture was stirred for 1.5 h at 0 °C or room temperature. After addition of pentane (1.2 mL), the mixture was filtered through silica gel (pentane) to provide the pyran.

Compound 5′: This compound was obtained from **3** in 95% yield (12.4 mg). Colorless oil. $[\alpha]_D^{23}$ = –20.8 (*c* = 0.60, $CHCl_3$). R_f = 0.59 (pentane/Et_2O, 97:3). ^{1}H NMR: δ = 1.00–1.31 (m, 5 H), 1.13 (d, *J* = 6.1 Hz, 3 H, C*H*$_3$), 1.26 (s, 3 H, C*H*$_3$), 1.41–1.73 (m, 11 H), 1.88–1.96 (m, 1 H), 3.73 (ddq, *J* = 6.1, 6.1, 2.4 Hz, 1 H, C*H*), 5.50 (m, 2 H, C*H*=C*H*) ppm. ^{13}C NMR: δ = 19.9, 20.7, 22.7, 26.1, 26.2, 32.9, 33.4, 34.9, 40.4, 66.3, 73.4, 132.9, 136.2 ppm. IR: $\tilde{\nu}$ = 2924, 2852, 1733, 1448, 1380, 1365, 1238, 1137, 1086, 1026, 969 cm^{-1}. MS (EI): *m*/*z* (%) = 222 (10.4) [M]$^+$, 207 (99), 153 (13.6), 139 (71.2), 135 (10.5), 125 (100), 113 (44.8), 112 (37.0), 99 (90.5). HRMS (EI): $C_{15}H_{26}O_2$ calcd. 222.1984; found 222.1981.

Compound 5: This compound was obtained from **3′** in 86% yield (11.2 mg). Colorless oil. $[\alpha]_D^{23}$ = –16.6 (*c* = 0.35, $CHCl_3$). R_f = 0.45 (pentane/Et_2O, 97:3). ^{1}H NMR: δ = 1.11–1.16 (m, 1 H), 1.11 (d, *J* = 6.2 Hz, 3 H, C*H*$_3$), 1.19 (s, 3 H, C*H*$_3$), 1.21–1.46 (m, 5 H), 1.51–1.59 (m, 3 H), 1.61–1.70 (m, 7 H), 1.93–2.03 (m, 1 H), 3.62 (ddq, *J* = 6.2, 6.2, 2.2 Hz, 1 H, C*H*), 5.31 (d, *J* = 16.7 Hz, 1 H, C*H*=C*H*), 5.43 (dd, *J* = 16.7, 6.2 Hz, 1 H, C*H*=C*H*) ppm. ^{13}C NMR: δ = 20.4, 22.5, 26.0, 26.2, 31.8, 33.1, 33.2, 33.4, 34.3, 40.6, 67.3, 74.5, 132.0, 136.3 ppm. IR: $\tilde{\nu}$ = 2925, 2852, 1732, 1447, 1366, 1282, 1211, 1055, 968 cm^{-1}. MS (EI): *m*/*z* (%) = 222 (5.4) [M]$^+$, 207 (100), 153 (14.9), 139 (81.5), 125 (59.0), 113 (25.3), 71 (67.9). HRMS (EI): $C_{15}H_{26}O_2$ calcd. 222.1984; found 222.1987.

Compound 6′: This compound was obtained from **4′** in 68% yield (6.6 mg). Colorless oil. R_f = 0.51 (pentane/Et_2O, 95:5). ^{1}H NMR: δ = 1.11 (d, *J* = 6.1 Hz, 3 H, C*H*$_3$), 1.14–2.17 (m, 12 H), 3.76 (ddq, *J* = 6.1, 6.1, 2.2 Hz, 1 H, C*H*), 5.82 (dt, *J* = 10.5, 3.8 Hz, 1 H, C*H*=C*H*), 6.21 (d, *J* = 10.5 Hz, 1 H, C*H*=C*H*) ppm. ^{13}C NMR: δ = 18.5, 19.4, 22.8, 26.1, 33.7, 36.0, 38.4, 66.1, 70.1, 127.6, 130.2 ppm. MS (EI): *m*/*z* = 166 [M$^+$]. HRMS *m*/*z* calcd. for $C_{15}H_{26}IO_2$ [M$^+$] 166.1358; found 166.1354. MS (EI): *m*/*z* = 166 (12.3) [M]$^+$, 138 (31.9), 97 (100), 68 (52.9). HRMS (EI): $C_{11}H_{18}O$ calcd. 166.1358; found 166.1354.

Compound 6: This compound was obtained from **4** in 68% yield (6.6 mg). Colorless oil. R_f = 0.31 (pentane/Et_2O, 95:5). ^{1}H NMR: δ = 1.02–1.20 (m, 1 H), 1.12 (d, *J* = 6.1 Hz, 3 H, C*H*$_3$), 1.26–1.86 (m, 9 H), 1.91–2.08 (m, 2 H), 3.73 (ddq, *J* = 6.1, 6.1, 1.8 Hz, 1 H, C*H*), 5.47 (d, *J* = 10.1 Hz, 1 H, C*H*=C*H*), 5.77 (dt, *J* = 10.1, 3.7 Hz, 1 H, C*H*=C*H*) ppm. ^{13}C NMR: δ = 19.1, 19.5, 22.9, 25.6, 28.7, 33.2, 34.5, 65.8, 71.5, 129.4, 134.5 ppm. MS (EI): *m*/*z* (%) = 166 (16.6) [M]$^+$, 151 (2.2), 138 (21.3), 97 (100), 68 (52.9). HRMS (EI): $C_{11}H_{18}O$ calcd. 166.1358; found 166.1350.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra of compounds **3**, **3′**, **4**, **4′**, **5**, **5′**, **6**, **6′**, **7**, **7′**, **8**, **8′**, **9**, **9′**, **10**, **11**, **12**, **13**, **13′**, **14**, and **14′**.

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[1] a) I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105–10146; b) R. Pradhan, M. Patra, A. K. Behera, B. K. Mishra, R. K. Behera, *Tetrahedron* **2006**, *62*, 779–828; c) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473–1482.

[2] H. Miyaoka, M. Shimomura, H. Kimura, Y. Yamada, *Tetrahedron* **1998**, *54*, 13467–13474.

[3] a) S. Sakemi, T. Higa, C. W. Jefford, G. Bernardinelli, *Tetrahedron Lett.* **1986**, *27*, 4287–4290; b) E. J. Corey, D.-C. Ha, *Tetrahedron Lett.* **1988**, *29*, 3171–3174.

[4] T. Suzuki, M. Suzuki, A. Furusaki, T. Matsumoto, A. Kato, Y. Imanaka, E. Kurosawa, *Tetrahedron Lett.* **1985**, *26*, 1329–1332.

[5] general review on the synthesis of tetrahydropyrans; a) M. C. Elliott, E. Williams, *J. Chem. Soc., Perkin Trans. 1* **2001**, 2303–2340; b) P. A. Clarke, S. Santos, *Eur. J. Org. Chem.* **2006**, 2045–2053.

[6] M. D. Morin, S. D. Rychnovsky, *Org. Lett.* **2005**, *7*, 2051–2053.

[7] H.-U. Lin, W.-P. Du, C.-C. Chang, C.-H. Lin, *Tetrahedron Lett.* **2005**, *46*, 5071–5076.

[8] a) H. Toshima, T. Goto, A. Ichihara, *Tetrahedron Lett.* **1995**, *36*, 3373–3374; b) C.-G. Yang, N. W. Reich, Z. Shi, C. He, *Org. Lett.* **2005**, *7*, 4553–4556; c) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285–2309.

[9] a) L. S. Hegedus, in: M. Schlosser, *Organometallics in Synthesis*, John Wiley and Sons, New York, **2002**, 2nd Ed., p. 1123; b) T. Hosokawa, S. Murahashi, *Intramolecular Oxypalladation*, in: E.-i. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, John Wiley and Sons, New York, **2002**, vol. 2, p. 2169; c) M. Miyazawa, Y. Hirose, M. Narantsetseg, H. Yokoyama, S. Yamaguchi, Y. Hirai, *Tetrahedron Lett.* **2004**, *45*, 2883–2886; d) S. Saito, T. Hara, N. Takahashi, M. Hirai, T. Moriwake, *Synlett* **1992**, 237–238.

[10] In comparison with other methods for the synthesis of tetrahydropyrans it is noteworthy that 2,6-*cis*- and -*trans*-substituted tetrahydropyrans are formed with similar efficiency. The synthesis of *trans*-tetrahydropyrans in particular is often not trivial (for a recent successful example, refer to S. Roth, C. B. W. Stark, *Angew. Chem. Int. Ed.* **2006**, *45*, 6218–6221.) a) J. Uenishi, M. Ohmi, A. Ueda, *Tetrahedron: Asymmetry* **2005**, *16*, 1299–1303; b) J. Uenishi, M. Ohmi, *Angew. Chem. Int. Ed.* **2005**, *44*, 2756–2760; c) N. Kawai, J. M. Lagrange, M. Ohmi, J. Uenishi, *J. Org. Chem.* **2006**, *71*, 4530–4537.

[11] D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807.

[12] Physical data for compound **7′**. Colorless oil. $[\alpha]_D^{22}$ = +19.9 (*c* = 1.00, $CHCl_3$). R_f = 0.34 (hexane/Et_2O, 75:25). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.05 (s, 6 H, C*H*$_3$Si), 0.89 (s, 9 H, C*H*$_3$CSi), 1.03–1.31 (m, 5H), 1.12 (d, *J* = 6.1 Hz, 3 H, C*H*$_3$), 1.43–1.86 (m, 11 H), 2.19–2.24 (m, 2 H), 3.80 (m, 1 H, C*H*OH), 4.13 (m, 1H, C*H*OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –4.8 (CH_3), –4.4 (CH_3), 18.1 (C), 18.8, 23.8, 25.0, 25.9, 25.9, 26.4, 28.1, 28.6, 38.8, 44.4, 67.4, 68.1, 80.3, 86.1 ppm. IR: $\tilde{\nu}$ = 3376, 2927, 2855, 1450, 1374, 1255, 1187, 1137, 1092, 1023, 893, 836, 774 cm^{-1}. MS (CI): *m*/*z* (%) = 339 (0.9) $[M + H]^+$, 321 (14.8), 281 (6.8), 189 (100). HRMS (CI): $C_{20}H_{39}O_2Si$ calcd. 339.2719; found 339.2712.

[13] In compounds **7**, **8**, **9**, **13**, **14**, and **4** there were no differences except for their degrees of optical rotation in the spectroscopic data for their (*R*) and (*S*) diastereoisomers.

[14] A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, Germany, **2004**, volumes 1 and 2.

[15] D. Kim, J. Lee, P. J. Shim, J. I. Lim, T. Doi, S. Kim, *J. Org. Chem.* **2002**, *67*, 772–781.

[16] Y. Kita, S. Matsuda, E. Fujii, M. Horai, K. Hata, H. Fujioka, *Angew. Chem. Int. Ed.* **2005**, *44*, 5857–5860.

[17] Their *de*s were less than 50%.

[18] E. J. Corey, J. Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012.

[19] After the transformation of the alcohols **13** and **13′** into the corresponding benzoates, diastereoselective ratios were determined by HPLC analysis (DAICEL CHIRALCEL AD-H). Eluent: hexane/propan-2-ol (99:1), flow rate: 0.1 mL min^{-1}, detection: 254 nm, retention time: 12.7 min [**13** (*R*) isomer], 19.1 min [**13′** (*S*) isomer].

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