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Highly Stereoselective Syntheses of All 1,2,3-*Me,OH,Me* Triads *via* Asymmetric Hydrogenation Reactions

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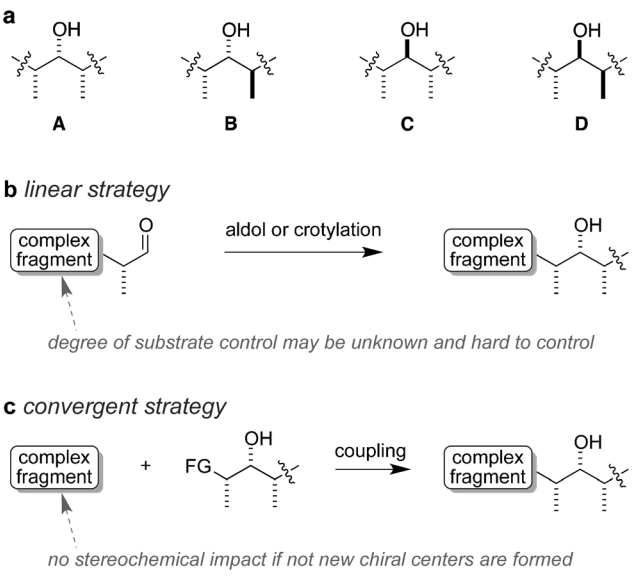
Abstract: Iridium-catalyzed asymmetric hydrogenations of chiral alkenes were used to access four pivotal α,ω-functionalized chirons, that contain widely occurring stereochemical 1,2,3-*Me,OH,Me* motifs. A chiral analogue of Crabtree's catalyst was used in key hydrogenation steps to form these motifs with high stereochemical purities. An application of one of these chirons is illustrated here with a synthesis of (−)-invictolide.

Keywords: asymmetric synthesis; catalysis; hydrogenation; iridium; polyketides

Introduction

Acyclic chains with 1,2,3-*Me,OH,Me* substituents (**A**–**D**) are found in many polyketide-derived materials.[1] Many strategies to access these stereochemical triads are *linear* as illustrated in Scheme 1, b.[2] Such approaches tend to be less efficient than convergent routes. More importantly, it can be difficult to find suitable reagents and conditions to effect linear transformations with high yields and stereoselectivities if the "complex fragment" has reactive functional groups and exerts significant substrate control.



Scheme 1. Routes to complex materials containing triads **A**–**D.**

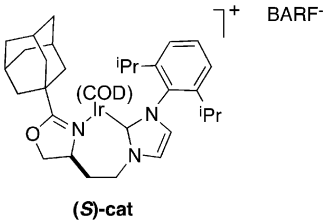
Convergent alternatives to incorporate the featured triads can involve construction of suitable chirons, then grafting them onto complex molecular fragments (Scheme 1, c). This strategy has advantages because stereocenters in the triads are set in the absence of the complex fragment. However, to generally implement this approach *all stereoisomers* of α,ω-bifunctional 1,2,3-*Me,OH,Me* triads have to be accessible. If that were accomplished in scalable, commercialized syntheses then this would facilitate syntheses of many polyketide-derived natural products.

Roche ester derivatives are excellent starting materials for syntheses of α,ω-functionalized species containing fragments **A**–**D**. So much work has been done in this area that it can only be outlined here. Methods to elaborate Roche ester derivative aldehydes into α,ω-functionalized chirons containing fragments **A**–**D** may be divided into: (i) reactions with chiral reagents for aldol or crotylation reactions;[3] (ii) aldol or crotylation reactions involving achiral reagents and chiral catalysts;[4] and (iii) routes relying mostly on substrate controlled diastereoselective reactions (Scheme 1, b).[5]

Relatively few methodologies, however, can be used to obtain *all* stereoisomers of α,ω-bifunctional 1,2,3-*Me,OH,Me* triads. For instance, none of the new catalyzed aldol or crotylation reactions will do this.[4] Methods that do give all the stereomers are restricted to those that feature resolved allenyl-stannane,[6] -silane,[5h,7] -zinc[8] and crotylsilane[9] reagents, or cro-

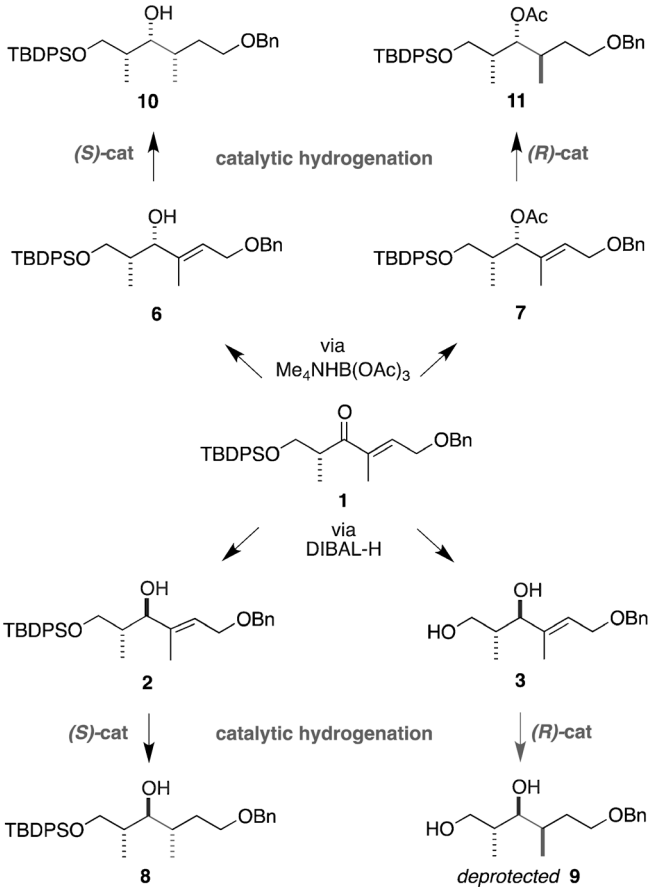
tylsilanes functionalized with chiral auxiliaries.[10] These methods have the compelling advantage that a C–C bond and two chiral centers are formed in one step. On the other hand, they have the disadvantages with respect to scale-up. This is because these methods involve multistep syntheses of optically active crotylation reagents and feature α-chiral aldehyde substrates that cannot be easily purified without degradation of optical purities.

In the work described here, the first objective was to establish methodology featuring alkene hydrogenations with **cat**[11] that would enable access to all four



(*S*)-cat

stereoisomers of α,ω-bifunctional 1,2,3-*Me,OH,Me* triads. The other objectives were to avoid stereochemically delicate Roche aldehyde derivatives, and to only use stoichiometric reagents that are commercially available and inexpensive enough to be used in large-scale work.



Scheme 2. Catalytic hydrogenation reactions to obtain α,ω-bifunctional 1,2,3-*Me,OH,Me* triads.

Results and Discussion

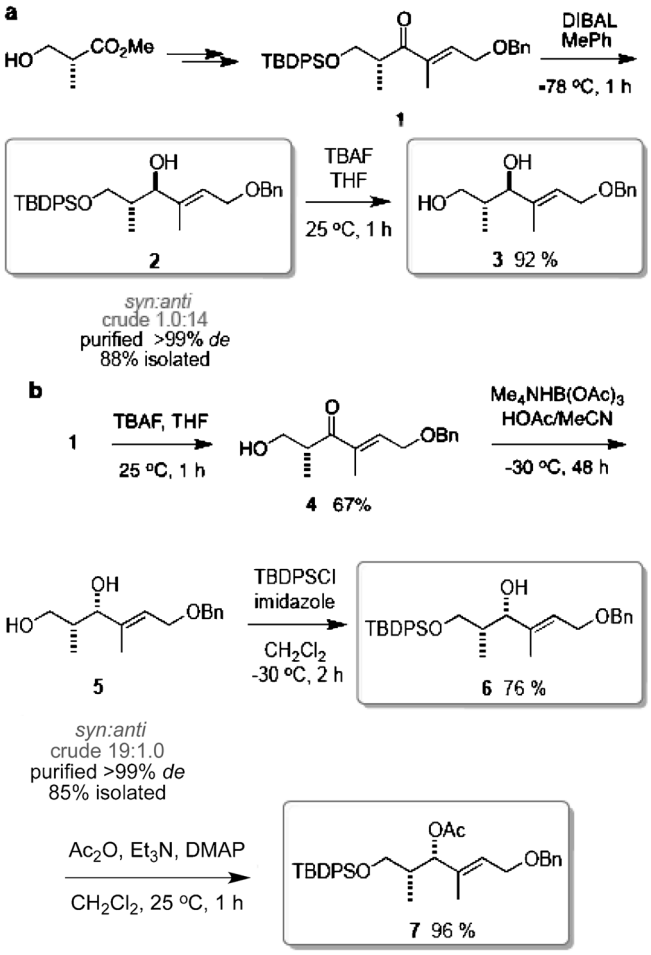
Scheme 2 outlines the strategy that guided the initial phase of this research, which, in fact, was successful. It involves formation of the carbon skeleton in key intermediate **1**, then reduction reactions to introduce the chiral centers.

Scheme 2 shows four key intermediates that preceded the hydrogenations steps: **2**, **3**, **6**, and **7**. To make these, a literature procedure[12] was adapted to allow the silyl ether **1** to be made in gram amounts (Scheme 3, a). This route involved protection of the Roche ester, reaction with a phosphonate-stabilized anion, and alkene formation. Ketone **1** can be obtained just as easily as the Roche aldehyde derivatives but, critically, it can be columned without loss of optical activity.

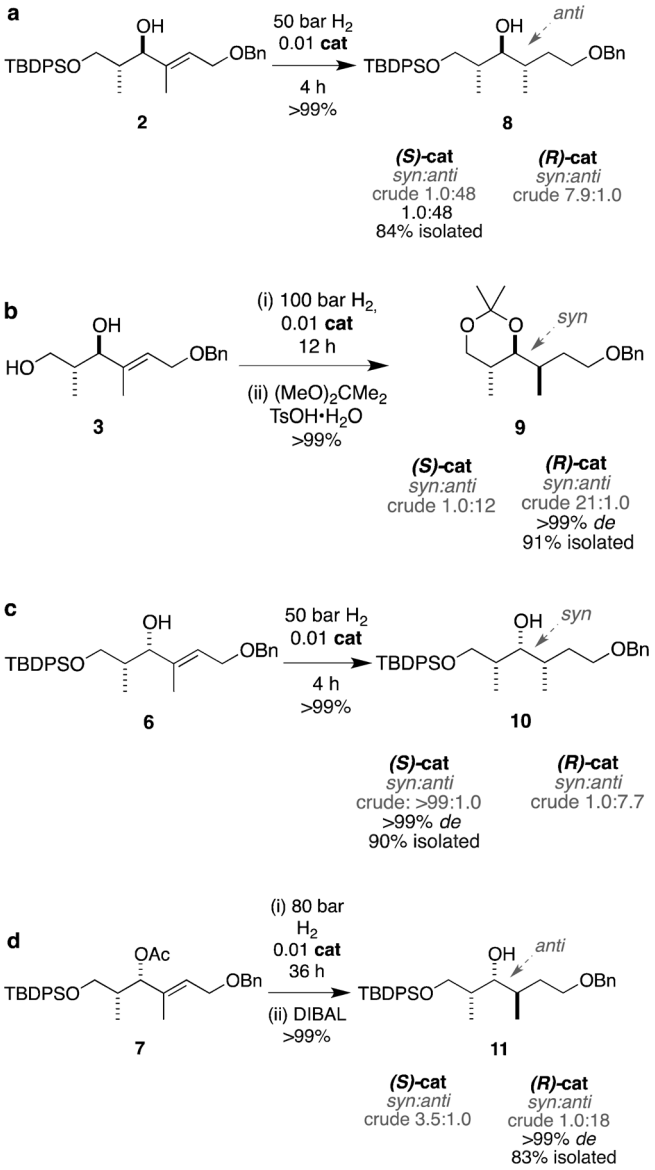
Felkin–Anh-selective DIBAL reduction of ketone **1** (by analogy with Boger[13]) gave the *anti*-alcohol **2** with high diastereoselectivity. The minor and major diastereomers produced were easily separated by column chromatography. Simple deprotection of compound **2** gave the diol **3**.

The routes that afford the key allylic alcohol derivatives **6** and **7** diverge from substrate **1**. Specifically, enone **1** was desilylated to allow chelation-controlled reduction of the corresponding 1,3-hydroxy ketone **4**,[13–14] affording the *syn*-alkenes **6** and **7** after some functional group manipulations (Scheme 3, b).

Alkenes **2**/**3**, and **6**/**7** have different protecting groups on the *same* scaffold. In fact, the protecting groups were varied throughout this study to enhance the stereoselectivities in the hydrogenations reactions; in total, 17 substrates were tested to reach this conclusion (see the Supporting Information). Scheme 4 shows data for hydrogenations of the key substrates with matched and mismatched catalysts; all these reactions were catalyst controlled. The *least* selective one (Scheme 4, d) gave a 1.0:18 bias in the crude reaction material, and the most (Scheme 4, c) gave only one diastereomer in our HPLC analysis (UV detection). In two cases (Scheme 4, b and d), it was convenient to modify the hydrogenation products to facilitate removal of trace stereoisomers by chromatography, but in the other two cases the stereoisomers could be separated directly, if necessary. Chirons **8**–**11** represent all the stereoisomers in the *Me,OH,Me* series, and each has differentially functionalized termini.



Scheme 3. The two key hydrogenation substrates for this study were formed *via* hydrides.



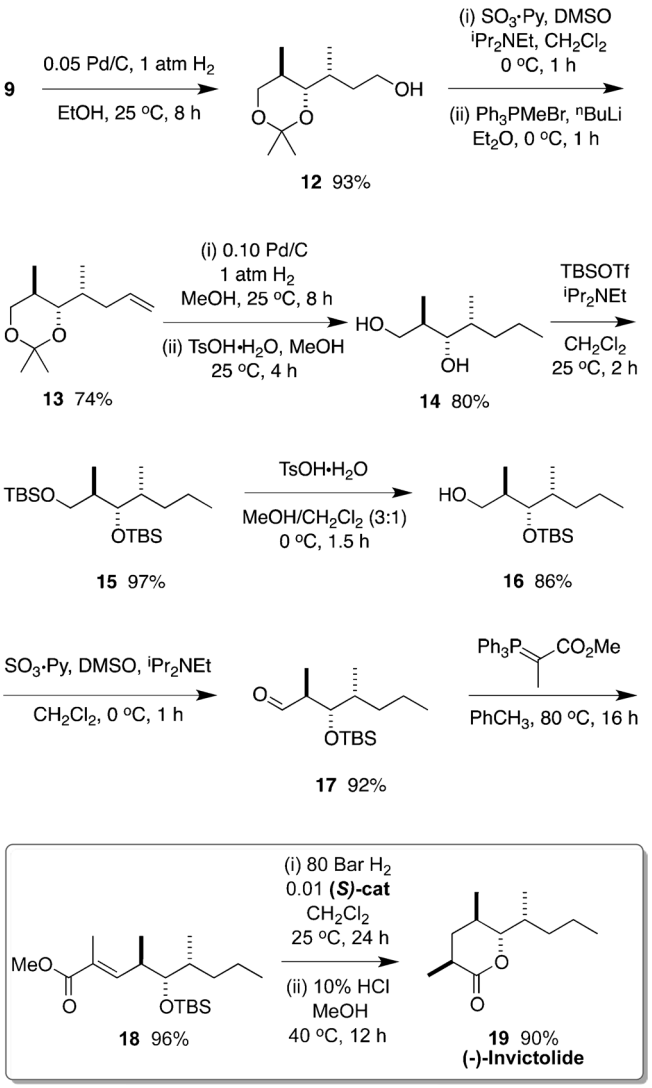
Scheme 4. Preparation of chirons for α,ω-functionalized triads: **a** *anti,anti*-type; **b** *anti,syn*; **c** *syn,syn*; and **d** *syn,anti*. All ratios quoted were from HPLC on a Chiralcel-OD column. All reactions were run in CH_2Cl_2 at 25 °C.

A synthesis of (−)-invictolide was performed to illustrate that these chirons can be used to prepare polyketide-derived natural products (Scheme 5). More than a gram of chiron **9** was prepared *via* the reaction indicated in Scheme 4, b. Debenzylation gave the alcohol **12**, which was then oxidized and homologated to alkene **13**. Reduction and deprotection of **13** gave the diol **14**; global silylation then selective desilylation of this gave the primary alcohol **16**.[15] Oxidation and reactions with a stabilized ylide gave the required alkene substrate **18**. Another diastereoselective hydrogenation, but to produce a 1,3-disposed dimethyl fragment,[16] was used to complete the construction of the chiral centers, before the last step in the synthesis: deprotection and cyclization to the lactone target.[17]

Conclusions

This work illustrates how chiral analogues of Crabtree's catalyst[18] can hydrogenate hindered alkenes even if they do not contain a group that typically coordinates to hydrogenation catalysts. **Cat** hydrogenates alkenes with selectivities that are usually high enough to override inherent biases of chiral substrates, i.e., catalyst control.[19] Substrate characteristics can be manipulated simply by varying protecting groups to optimize the stereoselectivities obtained. *Two* syntheses provided all *four* key substrates for the hydrogenation reactions, and all four of the targeted chirons were obtained with high stereoselectivities.

Two of the chiral centers in the invictolide synthesis above were derived from hydrogenation reactions, and there is at least the potential to prepare all the stereoisomers of the product using this route. Never-



Scheme 5. Total synthesis of (−)-invictolide *via* two hydrogenation steps mediated by **cat** (including the one used to make the starting material **9**).

theless, invictolide is a sub-optimal illustrative target because one of the terminal functional groups in the key chiron was not used, instead it was simply removed. More streamlined applications might involve homologation of both termini in different directions for syntheses of more complex materials; we have not yet demonstrated this, but propose to do so in further applications of this work.

Experimental Section

General Experimental Methods

All reactions were carried out under an atmosphere of dry nitrogen. Glassware was oven-dried prior to use. Unless otherwise indicated, common reagents or materials were obtained from commercial source and used without further purification. All the solvents were used after appropriate distillation or purification.

Flash column chromatography was performed using silica gel 60 (230–400 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck silica gel plates with QF-254 indicator and visualized by UV. Optical rotations were measured on Jasco DIP-360 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 (300 MHz ^{1}H; 75 MHz ^{13}C) or Varian Unity-500 (500 MHz ^{1}H; 125 MHz ^{13}C) spectrometer at room temperature. Chemical shifts are reported in ppm relative to the residual $CDCl_3$ ($\delta = 7.28$ ppm ^{1}H; $\delta = 77.26$ ppm ^{13}C). Coupling constants (J) are reported in Hertz. Iridium catalysts (*S*)-Cat and (*R*)-Cat were prepared using literature methods.[11b]

General Catalytic Hydrogenation Conditions

The alkene was dissolved in CH_2Cl_2 (0.5 M) and the iridium catalyst [(*S*)-Cat or (*R*)-Cat] (1 mol%) was then added. The resulting solution was degassed by three cycles of freeze-pump-thaw using nitrogen, then transferred to a Parr bomb. The bomb was flushed with hydrogen for 1 min without stirring. The mixture was then stirred at 700 rpm under 50 bar of H_2. After 4 h, the bomb was vented and the solvent was evaporated. The crude product was passed through a silica plug (EtOAc/hexanes = 3/7). The diastereomeric ratio of the crude material was then measured through chiral HPLC [The HPLC analysis was performed on a Beckman Series HPLC, UV detection monitored at wavelength 254 nm, using Chiralcel® OD (250 × 4.6 mm ID)].

(*R*)-*E*-6-(Benzyloxy)-1-[(*tert*-butyldiphenylsilyl)oxy]-2,4-dimethylhex-4-en-3-one (1)

n-BuLi (2.5 M in hexanes, 12.5 mL) was added to a solution of diethyl ethylphosphonate (5.66 g, 34.1 mmol) in THF (70 mL) at −78 °C over 10 min. The resulting mixture was stirred at −78 °C for 0.5 h. Then a solution of 3-(*tert*-butyldiphenylsilanyloxy)-2-(*R*)-methylpropionic acid methyl ester (4.86 g, 13.6 mmol) in THF (70 mL) was added to this mixture over 30 min. The solution was further stirred for 0.5 h at −78 °C and then $NH_4Cl(s)$ (50 mL) was added to quench the reaction. The mixture was warmed to 25 °C and diluted with H_2O (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried with Na_2SO_4, and concentrated under vacuum. Purification of the residue by flash chromatography on silica gel, eluting with EtOAc/hexanes (30:70) gave the desired phosphonate as a colorless oil; yield: 6.41 g (13.1 mmol, 96%). ^{1}H NMR indicated the product as a mixture of two diastereoisomers. The purified phosphonate (7.30 g, 14.9 mmol) was dissolved in THF (80 mL) and H_2O (2 mL). The solution was cooled to 0 °C and $Ba(OH)_2$ (2.55 g, 14.9 mmol) was added in one portion. The mixture was stirred for 0.5 h and then a solution of benzyloxyacetaldehyde (2.3 mL, 16.4 mmol) in THF (10 mL) was added dropwise. The resulting mixture was further stirred for 2 h at 25 °C before being quenched with $NaHCO_3(s)$ (50 mL). The mixture was diluted with Et_2O (50 mL) and the precipitates were removed *via* filtration on a Buchner funnel. The filtrate were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic

layers were dried with Na_2SO_4 and concentrated under vacuum. Purification of the residue by flash chromatography on silica gel, eluting with EtOAc/hexanes (5:95) gave enone **1** as a colorless oil; yield: 6.30 g (12.9 mmol, 87%); $[\alpha]_D^{21}$: −19.1 (*c* 0.83, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.60 (m, 4H), 7.41–7.26 (m, 11H), 6.72 (t, J = 4.5 Hz, 1H), 4.56 (s, 2H), 4.28–4.25 (m, 2H), 3.86–3.83 (m, 1H), 3.64–3.52 (m, 2H), 1.75 (s, 3H), 1.03 (d, J = 6.0 Hz, 3H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.6, 138.9, 137.9, 135.8, 135.8, 133.8, 133.6, 129.9, 128.8, 128.1, 128.1, 127.9, 73.3, 67.8, 67.2, 42.0, 27.0, 19.4, 14.7, 12.2; HR-MS (ESI): *m/z* = 487.2684, calcd. for $C_{31}H_{39}O_3Si$ $[M+H]^+$: 487.2668.

(2*R*,3*R*)-*E*-6-(Benzyloxy)-1-[(*tert*-butyldiphenylsilyl)-oxy]-2,4-dimethylhex-4-en-3-ol (2)

To a solution of enone **1** (4.31 g, 8.86 mmol) in toluene (100 mL) cooled to −78 °C was added the neat DIBAL (3.16 mL, 17.7 mmol) in a period of 5 min. The reaction mixture was stirred for an additional 2 h before dropwise addition of anhydrous EtOAc (5 mL) at −78 °C and transferred quickly into a vigorously stirred mixture of EtOAc/saturated potassium sodium tartrate aqueous solution (300 mL/100 mL). Stirring was continued for 1 h and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum. ^{1}H NMR of the crude product suggested the *syn*:*anti* diastereoisomer ratio was 1.0:14. After purification by flash chromatography on silica gel, eluting with EtOAc/hexanes (10:90), the desired *anti*-allylic alcohol **2** can be obtained with 88% isolated yield and the *syn*:*anti* diastereoisomer ratio was further increased to >99% *de* (check by HPLC). $[\alpha]_D^{20.6}$: −14.0 (*c* 0.71, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69–7.65 (m, 4H), 7.45–7.23 (m, 11H), 5.66 (t, J = 7.5 Hz, 1H), 4.51 (s, 2H), 4.11 (d, J = 10.0 Hz, 2H), 4.00 (d, J = 10.0 Hz, 1H), 3.90 (s, 1H), 3.80–3.78 (m, 1H), 3.67–3.63 (m, 1H), 1.96–1.89 (m, 1H), 1.64 (s, 3H), 1.06 (s, 9H), 0.73 (d, J = 5.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.0, 138.7, 135.8, 132.9, 128.1, 127.8, 124.8, 95.0, 83.2, 72.3, 69.2, 66.6, 37.5, 27.0, 19.3, 14.0, 11.8; HR-MS (ESI): *m/z* = 511.2633, calcd. for $C_{31}H_{40}NaO_3Si$ $[M+Na]^+$: 511.2644.

(2*R*,3*R*)-*E*-6-(Benzyloxy)-2,4-dimethylhex-4-ene-1,3-diol (3)

The allylic alcohol **2** (0.59 g, 1.2 mmol) was dissolved in THF (5 mL) followed by addition of TBAF (1 M in THF, 1.4 mL, 1.4 mmol). The resulting solution was stirred at 25 °C for 1 h, then the reaction was quenched by addition of $NH_4Cl(s)$ (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The organic extract was dried (Na_2SO_4) and concentrated under vacuum. Purification by flash column chromatography, eluting with EtOAc/hexanes (50:50) gave diol **3** as a colorless oil; yield: 0.30 g (1.2 mmol, 100%); $[\alpha]_D^{22.1}$: −11.0 (*c* 1.09, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5H), 5.62 (t, J = 6.0 Hz, 1H), 4.52 (s, 2H), 4.08–4.02 (m, 2H), 3.92 (d, J = 9.0 Hz, 1H), 3.74–3.61 (m, 2H), 2.93 (br, 1H), 2.60 (br, 1H), 1.97–1.85 (m, 1H), 1.65 (s, 3H), 0.75 (d, J = 9.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.2, 138.4, 128.7, 128.1, 128.0, 125.1, 84.4, 72.7, 68.4, 66.5, 37.4, 14.0, 11.6; HR-MS (ESI): *m/z* = 273.1472, calcd.: for $C_{15}H_{22}NaO_3$ $[M+Na]^+$: 273.1467.

(*R*)-*E*-6-(Benzyloxy)-1-hydroxy-2,4-dimethylhex-4-en-3-one (4)

The enone **1** (4.78 g, 9.8 mmol) was dissolved in THF (100 mL) followed by addition of TBAF (1 M in THF, 10.3 mL, 10.3 mmol). The resulting solution was stirred at 0 °C for 1 h, then the reaction was quenched by addition of $NH_4Cl(s)$ (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic extract was dried (Na_2SO_4) and concentrated under vacuum. Purification by flash column chromatography, eluting with EtOAc/hexanes (30:70) gave enone **4** as a colorless oil; yield: 1.60 g (6.6 mmol, 67%); $[\alpha]_D^{22.2}$: −12.5 (*c* 1.27, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.26 (m, 5H), 6.78–6.72 (m, 1H), 4.58 (s, 2H), 4.30–4.22 (m, 2H), 3.92–3.64 (m, 2H), 3.47–3.35 (m, 1H), 2.21 (t, J = 6.0 Hz, 1H), 1.74 (s, 3H), 1.13 (d, J = 9.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.0, 137.8, 136.9, 128.8, 128.2, 128.1, 73.4, 67.7, 65.1, 41.5, 15.3, 12.1 (missing the peak for the carbonyl carbon); HR-MS (ESI): *m/z* = 249.1488, calcd. for $C_{15}H_{21}O_3$ $[M+H]^+$: 249.1491.

(2*R*,3*S*)-*E*-6-(Benzyloxy)-2,4-dimethylhex-4-ene-1,3-diol (5)

Tetramethylammonium triacetoxyborohydride (13.9 g, 52.8 mmol) was dissolved in CH_3CN/AcOH (60 mL, 1:1) and the mixture was stirred for 30 min at 25 °C. The resulting clear solution was cooled to −30 °C and a solution of **4** in MeCN (6 mL, 2 × 2 mL for rinse) was added dropwise. The reaction mixture was stirred at −30 °C for an additional 48 h before dropwise addition of saturated potassium sodium tartrate aqueous solution (20 mL). Stirring was continued for 1 h and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with $NaHCO_3(s)$ (30 mL), brine (30 mL) and then dried with Na_2SO_4. The solution was concentrated under vacuum. Purification by flash column chromatography, eluting with EtOAc/hexanes (50:50 to 80:20) gave diol **5** as a colorless oil; yield: 1.40 g (5.6 mmol, 81%). ^{1}H NMR of the crude product indicated the *syn*:*anti* diastereoisomer ratio was >19:1.0. $[\alpha]_D^{21.9}$: −32.2 (*c* 0.62, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 5H), 5.70 (t, J = 6.0 Hz, 1H), 4.53 (s, 2H), 4.18–4.08 (m, 3H), 3.72–3.64 (m, 2H), 2.07–1.83 (m, 3H), 1.63 (s, 3H), 0.91 (d, J = 9.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.8, 138.6, 128.7, 128.1, 127.9, 121.9, 78.4, 72.6, 67.1, 66.5, 37.7, 13.9, 10.6; HR-MS (ESI): *m/z* = 273.1463, calcd. for $C_{15}H_{22}NaO_3$ $[M+Na]^+$ 273.1467.

(2*R*,3*S*)-*E*-6-(Benzyloxy)-1-[(*tert*-butyldiphenylsilyl)-oxy]-2,4-dimethylhex-4-en-3-ol (6)

To a solution of compound **5** (0.88 g, 3.5 mmol) and imidazole (0.26 g, 3.85 mmol) in CH_2Cl_2 (10 mL) was added a solution of TBDPSCl (1.02 g, 3.7 mmol) in CH_2Cl_2 (5 mL, 2 × 1 mL for rinse) dropwise at −30 °C. The reaction was stirred for 2 h, then quenched with $NaHCO_3(s)$ (10 mL). The organic layer was separated and the aqueous layer was ex-

tracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum. Purification by flash column chromatography, eluting with EtOAc/hexanes (20:80) gave alcohol **6** as a colorless oil; yield: 1.30 g (2.7 mmol, 76%); $[\alpha]_D^{22.2}$: −15.0 (*c* 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.65 (m, 4H), 7.47–7.26 (m, 11H), 5.74 (t, *J* = 6.0 Hz, 1H), 4.51 (s, 2H), 4.28 (m, 1H), 4.09 (d, *J* = 6.0 Hz, 2H), 3.72–3.64 (m, 2H), 2.42 (d, *J* = 3.0 Hz, 1H), 1.91–1.82 (m, 1H), 1.58 (s, 3H), 1.08 (s, 9H), 0.90 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.2, 138.7, 135.8, 133.4, 130.0, 128.0, 127.8, 121.9, 77.4, 72.3, 67.9, 66.5, 37.9, 27.1, 19.5, 13.8, 10.5; HR-MS (ESI): *m/z* = 489.2848, calcd. for $C_{31}H_{41}O_3Si$ $[M+H]^+$: 489.2825.

(2*R*,3*S*)-*E*-6-(Benzyloxy)-1-[(*tert*-butyldiphenylsilyl)-oxy]-2,4-dimethylhex-4-en-3-yl Acetate (7)

To a solution of compound **6** (0.86 g, 1.75 mmol) and DMAP (22 mg, 0.18 mmol) in CH_2Cl_2 (10 mL) was added Ac_2O (0.33 mL, 3.5 mmol) and Et_3N (0.49 mL, 3.5 mmol) dropwise at 25 °C. The reaction was stirred for 1 h, and then quenched with $NaHCO_3(s)$ (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum. Purification by flash column chromatography, eluting with EtOAc/hexanes (5:95) gave acetate **7** as a colorless oil; yield: 0.85 g (1.6 mmol, 92%); $[\alpha]_D^{20.8}$: −20.6 (*c* 0.87, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.60 (m, 4H), 7.43–7.26 (m, 11H), 5.53 (t, *J* = 6.0 Hz, 1H), 5.31 (d, *J* = 3.0 Hz, 1H), 4.44 (s, 2H), 4.11–3.97 (m, 2H), 3.49 (d, *J* = 9.0 Hz, 2H), 2.05 (s, 3H), 2.04–1.96 (m, 1H), 1.56 (s, 3H), 1.05 (s, 9H), 0.89 (d, *J* = 9.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 138.5, 136.4, 135.9, 135.8, 133.9, 133.8, 127.8, 123.6, 77.8, 77.5, 72.1, 66.3, 65.6, 37.7, 27.1, 21.3, 19.5, 13.8, 11.7; HR-MS (ESI): *m/z* = 553.2765, calcd. for $C_{33}H_{42}NaO_4Si$ $[M+Na]^+$: 553.2750.

(2*R*,3*S*,4*S*)-6-(Benzyloxy)-1-[(*tert*-butyldiphenylsilyl)-oxy]-2,4-dimethylhexan-3-ol (8)

Hydrogenation of **2** (175 mg, 0.36 mmol) was carried out according to the general procedure using **(*S*)-Cat.** (1 mol%, 6 mg) in CH_2Cl_2 (0.72 mL). NMR of the crude product showed 100% reduction. HPLC analysis of the crude material showed *syn:anti* ratio to be 1.0:48. One simple column chromatography on silica gel, eluting with EtOAc/hexanes (5:95) gave *anti,anti* triad **8** (*syn:anti* = 1.0:48 from HPLC analysis) as a colorless oil; yield: 155 mg (0.32 mmol, 89%); $[\alpha]_D^{20.8}$: −21.7 (*c* 0.92, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.66 (m, 4H), 7.49–7.27 (m, 11H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 3.80–3.36 (m, 6H), 1.99–1.79 (m, 3H), 1.61–1.53 (m, 1H), 1.07 (s, 9H), 0.99 (d, *J* = 6.0 Hz, 3H), 0.87 (d, *J* = 9.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.9, 135.8, 133.1, 130.1, 128.6, 128.0, 128.0, 127.8, 127.7, 81.1, 73.1, 69.2, 69.0, 37.5, 33.2, 30.3, 27.1, 19.4, 17.3, 14.2; HR-MS (ESI): *m/z* = 491.3002, calcd. for $C_{31}H_{43}O_3Si$ $[M+H]^+$: 491.2981.

(4*S*,5*R*)-4-[(*R*)-4-(Benzyloxy)butan-2-yl]-2,2,5-trimethyl-1,3-dioxane (9)

Hydrogenation of **3** (310 mg, 1.2 mmol) was carried out according to the general procedure using **(*R*)-Cat** (1 mol%, 19 mg) in CH_2Cl_2 (1 mL). NMR of the crude product showed 100% conversion. Thus without purification, the crude diol was dissolved in CH_2Cl_2 (10 mL). TsOH (22.8 mg, 0.12 mmol) and 2,2-Dimethoxypropane (0.74 mL, 6.0 mmol) were then added to the solution of diol and the resulting mixture was stirred for 1 h at 25 °C. The reaction was quenched by adding $NaHCO_3(s)$ (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum. HPLC analysis of the crude material showed *syn:anti* ratio to be 21:1.0. Purification by column chromatography EtOAc/hexanes (5:95) gave the *anti,syn* triad **9**[20] as a colorless oil; yield: 319 mg (91% from **3**); HPLC analysis showed *syn:anti* >99% *de*; $[\alpha]_D^{21.1}$: −34.7 (*c* 0.92, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 3.70–3.65 (m, 1H), 3.56–3.36 (m, 4H), 1.97–1.60 (m, 4H), 1.34 (s, 3H), 1.33 (s, 3H), 0.88 (d, *J* = 6.0 Hz, 3H), 0.72 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.9, 128.6, 128.0, 127.8, 98.3, 76.7, 73.2, 68.4, 66.7, 33.8, 31.1, 30.1, 29.9, 19.2, 12.7, 12.5.

(2*R*,3*R*,4*S*)-6-(Benzyloxy)-1-[(*tert*-butyldiphenylsilyl)-oxy]-2,4-dimethylhexan-3-ol (10)

Hydrogenation of **6** (250 mg, 0.50 mmol) was carried out according to the general procedure using **(*S*)-Cat.** (1 mol%, 8 mg) in CH_2Cl_2 (1.0 mL). NMR of the crude product showed 100% reduction to **10**. HPLC analysis of the crude material can only detect the *syn,syn* triad. One simple column chromatography on silica gel, eluting with EtOAc/hexanes (5:95) give *syn,syn* triad **10** as a colorless oil; yield: 230 mg (0.45 mmol, 90%); $[\alpha]_D^{21.1}$: −8.9 (*c* 0.89, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71–7.65 (m, 4H), 7.48–7.29 (m, 11H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 3.73–3.47 (m, 5H), 2.72 (d, *J* = 3.0 Hz, 1H), 1.91–1.69 (m, 3H), 1.46–1.37 (m, 1H), 1.08 (s, 9H), 1.01 (d, *J* = 6.0 Hz, 3H), 0.96 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6, 135.8, 133.4, 130.0, 130.0, 128.6, 128.0, 127.9, 127.8, 77.5, 73.3, 68.8, 68.6, 37.2, 33.6, 33.5, 27.1, 19.5, 15.1, 11.3; HR-MS (ESI): *m/z* = 491.2995, calcd. for $C_{31}H_{43}O_3Si$ $[M+H]^+$: 491.2981.

(2*R*,3*R*,4*R*)-6-(Benzyloxy)-1-[(*tert*-butyldiphenylsilyl)-oxy]-2,4-dimethylhexan-3-ol (11)

Hydrogenation of **7** (440 mg, 0.83 mmol) was carried out according to the general procedure using **(*R*)-Cat** (1 mol%, 15 mg) in CH_2Cl_2 (1.5 mL). NMR of the crude product showed 100% conversion. Thus without purification, the crude acetate was dissolved in CH_2Cl_2 (10 mL) and cooled to −78 °C. DIBAL-H (1.0 M in hexanes, 2.0 mL, 2.0 mmol) was added dropwise and the solution was stirred at −78 °C for 1 h. EtOAc (2 mL) was added to the mixture followed by addition of saturated potassium sodium tartrate aqueous solution (5 mL). Stirring was continued for 1 h and the layers were separated. The aqueous layer was extracted with

EtOAc (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum. HPLC analysis of the crude material showed *syn:anti* ratio to be 1.0:18. Purification by column chromatography EtOAc/hexanes (5:95) gave the *syn,anti* triad **11** as a colorless oil; yield: 340 mg (0.69 mmol, 83% from **7)**: HPLC analysis showed *syn:anti* >99% *de*; $[\alpha]_D^{21.4}$: −5.5 (*c* 1.08, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.70–7.65 (m, 4H), 7.45–7.28 (m, 11H), 4.55 (d, *J*=12.0 Hz, 1H), 4.51 (d, *J*=12.0 Hz, 1H), 3.73–3.51 (m, 5H), 3.00 (d, *J*=3.0 Hz, 1H), 1.99–1.51 (m, 4H) (integrated with a huge H_2O peak), 1.08 (s, 9H), 0.93 (d, *J*=6.0 Hz, 3H), 0.85 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=138.7, 135.9, 133.6, 130.0, 129.9, 128.6, 127.9, 127.9, 127.8, 77.5, 73.2, 68.9, 68.9, 37.0, 34.3, 33.4, 27.2, 19.5, 16.7, 9.6; HR-MS (ESI): *m/z*=491.2969, calcd. for $C_{31}H_{43}O_3Si$ $[M+H]^+$: 491.2981.

(*R*)-3-[(4*S*,5*R*)-2,2,5-Trimethyl-1,3-dioxan-4-yl]butan-1-ol (12)

To a solution of **9** (1.06 g, 3.64 mmol) in MeOH (20 mL) was added Pd/C (10% on carbon, 194 mg, 0.18 mmol) in one portion. The air inside the reaction flask was vacuumed out and then hydrogen gas was purged into the flask. The mixture was stirred under 1 atm H_2 pressure at room temperature for 8 h. The mixture was filtered on a plug of silica gel (5 cm), washed with MeOH, and concentrated to give free saturated alcohol **12** as a colorless oil; yield: 0.68 g (93%); $[\alpha]_D^{22.0}$: −42.8 (*c* 0.70, $CHCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.78–3.65 (m, 3H), 3.61–3.46 (m, 2H), 2.14–2.10 (m, 1H), 2.01–1.89 (m, 2H), 1.85–1.59 (m, 2H), 1.43 (s, 3H), 1.38 (s, 3H), 0.93 (d, *J*=6.0 Hz, 3H), 0.75 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=98.5, 77.9, 66.5, 60.4, 37.3, 31.1, 30.8, 29.9, 19.3, 12.7, 12.4; HR-MS (ESI): *m/z*=203.1654, calcd. for $C_{11}H_{23}O_3$ $[M+H]^+$: 203.1647.

(4*S*,5*R*)-2,2,5-Trimethyl-4-[(*R*)-pent-4-en-2-yl]-1,3-dioxane (13)

The alcohol **12** (0.68 g, 2.0 mmol) was dissolved in CH_2Cl_2 (60 mL) at 0°C. DMSO (6.0 mL, 84.5 mmol) and DIPEA (5.9 mL, 33.8 mmol) were added. To this solution at 0°C, SO_3·Py complex (2.69 g, 16.9 mmol) was added and the resulting solution was stirred at that temperature for 1 h. The reaction was quenched with NH_4Cl(*s*) (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic solution was dried (Na_2SO_4) and concentrated under vacuum. The resulting residue was carried out to the next step without any further purification. In a separate round-bottom flask, methyltriphenylphosphonium bromide (2.41 g, 6.76 mmol) suspension in THF (20 mL) was cooled to 0°C and *n*-BuLi (2.0 M in pentane, 3.4 mL, 6.8 mmol) was added dropwise. The reaction was stirred for 0.5 h before the crude aldehyde in THF solution (8 mL, 2× 1 mL for rinsing) was cannulated. After 1 h, saturated NH_4Cl aqueous solution (10 mL) was added and the mixture was stirred and allowed to warm to 25°C. The layers were then separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuu, at 10°C. Purification by flash column chromatography, eluting with Et_2O/pentane (5:95) gave alkene **13** as a colorless oil; yield: 0.49 g (74% over two steps); $[\alpha]_D^{19.6}$: −27.1 (*c* 0.81, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.86–5.72 (m, 1H), 5.06–4.96 (m, 2H), 3.71 (dd, *J*=3.0, 12.0 Hz, 1H), 3.54–3.45 (m, 2H), 2.22–1.70 (m, 4H), 1.40 (s, 3H), 1.38 (s, 3H), 0.90 (d, *J*=9.0 Hz, 3H), 0.71 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=138.2, 116.0, 98.3, 76.2, 66.7, 38.5, 33.6, 31.1, 30.0, 19.3, 12.8, 12.5; HR-MS (ESI): *m/z*=199.1670, calcd. for $C_{12}H_{23}O_2$ $[M+H]^+$: 199.1698.

(2*R*,3*S*,4*R*)-2,4-Dimethylheptane-1,3-diol (14)

To a solution of **13** (0.49 g, 2.5 mmol) in MeOH (10 mL) was added Pd/C (10% on carbon, 266 mg, 0.25 mmol) in one portion. The air inside the reaction flask was vacuumed out and then hydrogen gas was purged into the flask. The mixture was stirred under 1 atm H_2 pressure at room temperature for 8 h. The mixture was filtered on a plug of silica gel (5 cm) and washed with MeOH (5 mL). To the filtrate the TsOH (48 mg, 0.25 mmol) was added in one portion and the solution was stirred for 4 h at 25°C. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), extracted with ether (3×10 mL), dried over $MgSO_4$, and concentrated. Purification by column chromatography (silica gel, EtOAc/hexanes, 50:50) gavediol **14** as a colorless liquid; yield: 0.32 g (80%, 2 steps); $[\alpha]_D^{21.7}$: −21.9 (*c* 0.73, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.79–3.63 (m, 2H), 3.53–3.47 (m, 1H), 2.94–2.91 (m, 1H), 2.34 (d, *J*=6.0 Hz, 1H), 1.96–1.82 (m, 1H), 1.67–1.60 (m, 1H), 1.41–1.24 (m, 4H), 0.94 (t, *J*=6.0 Hz, 3H), 0.90 (d, *J*=9.0 Hz, 3H), 0.84 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=80.7, 69.1, 37.7, 36.5, 35.1, 20.7, 14.5, 13.8, 12.5; HR-MS (ESI): *m/z*=161.1535, calcd. for $C_9H_{21}O_2$ $[M+H]^+$: 161.1542.

(5*S*,6*R*)-2,2,3,3,6,9,9,10,10-Nonamethyl-5-[(*R*)-pentan-2-yl]-4,8-dioxa-3,9-disilaundecane (15)

The diol **14** (0.32 g, 2.0 mmol) was dissolved in CH_2Cl_2 (10 mL). TBSOTf (1.15 mL, 5.0 mmol) and *i*Pr_2NEt (1.05 mL, 6.0 mmol) were added sequentially. The solution was stirred at 25°C for 2 h, and then the reaction was quenched by adding NH_4Cl(*s*) (10 mL). The mixture was diluted with CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification by column chromatography (silica gel, hexanes) gave **15** as a colorless liquid; yield: 0.75 g (1.94 mmol, 97%); $[\alpha]_D^{20.9}$: +12.3 (*c* 0.65, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (dd, *J*=5.0, 10.0 Hz, 1H), 3.51–3.50 (m, 1H), 3.42 (dd, *J*=5.0, 10.0 Hz, 1H), 1.83–1.78 (m, 1H), 1.63–1.53 (m, 1H), 1.34–1.13 (m, 4H), 0.91–0.89 (m, 36H), 0.86 (d, *J*=5.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=77.2, 65.9, 40.6, 37.4, 36.0, 26.4, 26.2, 26.0, 21.0, 18.6, 14.8, 14.6, 14.5, −2.7, −3.6, −3.7, −5.0, −5.1; HR-MS (ESI): *m/z*=389.3257, calcd. for $C_{21}H_{49}O_2Si$ $[M+H]^+$: 389.3271.

(2*R*,3*S*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2,4-dimethylheptan-1-ol (16)

The silyl ether **15** (0.70 g, 1.8 mmol) was dissolved in CH_2Cl_2/MeOH (20 mL, 1/3) at 0°C. TsOH (34 mg, 0.18 mmol) was added in one portion. The resulting solution was stirred at that temperature for 1 h. Et_3N (5 mL) was then added to the reaction and all the solvents were evapo-

rated under vacuum. The residue was purified though column chromatography, eluting with EtOAc/hexanes (10:90) to give desired primary alcohol as a colorless liquid; yield: **16** (0.42 g (1.55 mmol, 86%); $[\alpha]_D^{21.5}$: 13.9 (*c* 1.15, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.68$–3.58 (m, 2H), 3.52 (dd, $J = 5.0$, 10.0 Hz, 1H), 2.63 (t, $J = 7.5$ Hz, 1H), 1.91–1.84 (m, 1H), 1.66–1.61 (m, 1H), 1.47–1.37 (m, 2H), 1.24–1.13 (m, 2H), 0.98 (d, $J = 5.0$ Hz, 3H), 0.94–0.90 (m, 15H), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 81.5, 66.5, 38.4, 37.8, 35.6, 26.3, 21.1, 18.5, 16.6, 15.4, 14.6, −3.7, −3.9; HR-MS (ESI): $m/z = 275.2419$, calcd. for $C_{15}H_{35}O_2Si$ $[M+H]^+$: 275.2406.

(4*R*,5*S*,6*R*,*E*)-Methyl 5-[(*tert*-butyldimethylsilyl)oxy]-2,4,6-trimethylnon-2-enoate (18)

The alcohol **16** (275 mg, 1.0 mmol) was dissolved in CH_2Cl_2 (30 mL) at 0 °C. DMSO (0.11 mL, 1.5 mmol) and DIPEA (0.87 mL, 5.0 mmol) were added. To this solution SO_3·Py complex (478 mg, 3.0 mmol) was added and the resulting solution was stirred at that temperature for 1 h. The reaction was quenched with $NH_4Cl(s)$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3× 20 mL). The combined organic solution was dried (Na_2SO_4) and concentrated under vacuum. Without any further purification, the resulting crude aldehyde was immediately dissolved in toluene (10 mL) and the Wittig reagent (1.74 g, 5.0 mmol) was added in one portion at 25 °C. The reaction mixture was then put on an oil bath (preheated to 80 °C) and stirred for 16 h. After being cooled to 25 °C, the reaction mixture was diluted with hexanes (80 mL) and filtrated through Celite. The filtrate was concentrated and purification of the residue by flash chromatography on silica gel, eluting with EtOAc/hexanes (5:95) gave alkene **18** as a colorless oil; yield: 300 mg (0.88 mmol, 88%); $[\alpha]_D^{21}$: 20.9 (*c* 0.86, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.85$ (d, $J = 9.0$ Hz, 1H), 3.76 (s, 3H), 3.50–3.46 (m, 1H), 2.77–2.65 (m, 1H), 1.86 (s, 3H), 1.39–1.00 (m, 4H), 0.93 (d, $J = 6.0$ Hz, 3H), 0.90(s, 9H), 0.91–0.88 (m 3H), 0.87 (t, $J = 9.0$ Hz, 3H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.1$, 146.6, 126.3, 79.7, 51.9, 37.5, 37.5, 36.2, 26.3, 21.0, 18.1, 15.0, 14.5, 12.8, −3.5, −3.7; HR-MS (ESI): $m/z = 343.2679$, calcd. for $C_{19}H_{39}O_3Si$ $[M+H]^+$: 343.2668.

(−)-Invictolide (19)

Hydrogenation of **18** (200 mg, 0.58 mmol) was carried out according to the general procedure using **(*S*)-Cat.** (11 mol%, 10 mg) in CH_2Cl_2 (1.0 mL). NMR of the crude product showed 100% reduction. ^{1}H NMR analysis of the crude material showed >19:1.0 diastereoselectivity for the hydrogenation. After hydrogenation the solvent was evaporated. Then the crude oil was dissolved in MeOH (4 mL) followed by addition of 10% HCl(aq) (0.2 mL). The resulting solution was stirred at 40 °C for 12 h, and then the reaction was cooled to 25 °C and quenched by addition of $NaHCO_3(s)$ (5 mL). The solution was diluted by addition of Et_2O (20 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3×10 mL). The organic extract was dried (Na_2SO_4) and concentrated under vacuum. Purification by flash column chromatography, eluting with Et_2O/pentane (10:90) gave (−)-invictolide **19**[17c] as a colorless oil; yield: 104 mg (0.52 mmol, 90%); $[\alpha]_D^{21}$: −99.7 (*c* 0.77, $CHCl_3$) {lit.[17e] $[\alpha]_D$: −99.2 (*c* 0.7, $CHC1_3$)}. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.92$ (d, $J = 10.0$ Hz, 1H), 2.69–2.62 (m, 1H), 2.05–1.95 (m, 1H), 1.69 (t, $J = 10.0$ Hz, 2H), 1.38–1.27 (m, 5H), 1.23 (d, $J = 10.0$ Hz, 3H), 0.99 (d, $J = 5.0$ Hz, 3H), 0.92 (t, $J = 5.0$ Hz, 3H), 0.88 (d, $J = 12.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 176.7$, 85.7, 36.1, 35.4, 33.6, 32.5, 28.4, 20.4, 16.6, 14.1, 12.3; HR-MS (ESI): $m/z = 199.1691$, calcd. for $C_{12}H_{23}O_2$ $[M+H]^+$: 199.1698.

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