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1,2-Induction in Intramolecular Diene Cyclozirconation: Control of Relative Configuration

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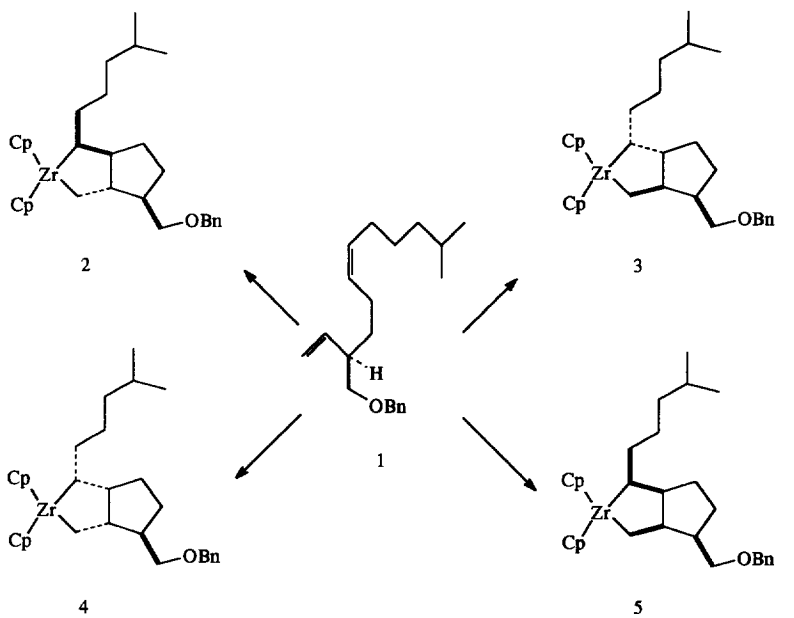
Abstract: We have observed that cyclozirconation of a diene having a substituent on the bridge connecting the two alkenes leads to a single predominant zirconacycle with control of three new stereogenic centers.

In 1989, we[1] and Negishi[2] independently reported that reduction[3] of zirconocene dichloride in the presence of a simple 1,6- or 1,7-diene led to ring formation, often with excellent stereochemical control.[4,5] To be truly useful, cyclozirconation should allow the diastereoselective construction of more substituted cycloalkanes.[6,7] Because two new stereogenic centers are expected in the cyclozirconation of **1**, four diastereomeric products (**2** - **5**) are possible. We now report that cyclozirconation of a diene having a substituent on the bridge connecting the two alkenes leads to a single predominant product zirconacycle with control of three new stereogenic centers (**1** → **2**).



RESULTS AND DISCUSSION

Dianion coupling[8] of methallyl alcohol **11** to the chloride[9] derived from the alcohol **10**, prepared by a modification of the literature procedure,[10] provided the allylic alcohol **12** (**Scheme 1**). The epoxy alcohol was prepared by catalytic Sharpless asymmetric epoxidation.[11] The enantiomerically enriched epoxide (5:1) was reduced at the more hindered site using the Hutchins procedure ($NaBH_3CN/BF_3OEt_2$).[12a,13] The procedure called for the slow addition of BF_3OEt_2 to the reaction. However, in practice we found that the yield was better if it was added all at once.

We observed that the derived primary alcohol **14** was nonracemic. No attempt has been made to optimize the Sharpless epoxidation. The ^{13}C spectra of the benzyl protected epoxy alcohol **13** and the reduced alcohol **14** were analyzed in the presence of a chiral Europium shift reagent [$Eu(hfc)_3$]. A comparison was made to the corresponding racemic material (from vanadyl acetylacetonate/TBHP and reduction).[14] Our synthetic epoxide and alcohol each had an enantiomeric ratio of 5:1.[13]

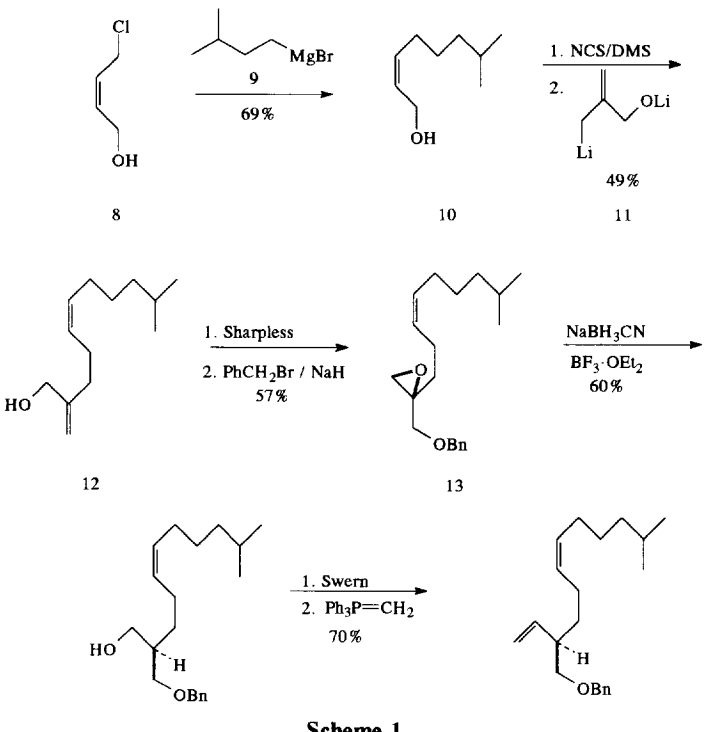
The diene synthesis was completed by oxidizing the primary alcohol **14** by the Swern procedure,[15] followed by a one carbon Wittig coupling. We found that the intermediate aldehyde was unstable to silica gel chromatography, but that the crude reaction mixture from the Swern oxidation could be added directly to excess ylide to accomplish the desired homologation.

The intramolecular cyclozirconation of diene **15** would create three new stereogenic centers, and so eight diastereomers. In fact, we observed on cyclozirconation and oxygenation a major and a minor diastereomer (**6** and **7**) in a 58% yield with a ratio of 3:1 (**Scheme 2**).

A series of experiments was run to optimize this cyclozirconation. The time for stirring the reaction varied from 2 h to 29 h. The best yields were obtained from runs lasting between 8 and 16 h. Runs of less than 8 h tended to have diminished yields. Warming the reaction mixture (75°C, 2 h) proved to be counterproductive. No product diol was isolated, but instead decomposed diene and benzyl alcohol were recovered.

The intermediate zirconacycle was subjected to a stream of O_2 (passed through a drying tube as prescribed by Schwartz[16]) at 0°C. The time of the oxygenation period was varied from 5 minutes to 1.5 h. A period of 6 minutes proved to be sufficient to maximize the yield of the product diol.

During the oxygenation period with O_2, the reaction turned from a red-brown color to a light yellow, with solids precipitating. These solids tended to make product isolation difficult, leading to emulsions on acidification. In practice we found that stirring with sodium borohydride prior to acidification broke up the solids, making product isolation more efficient.

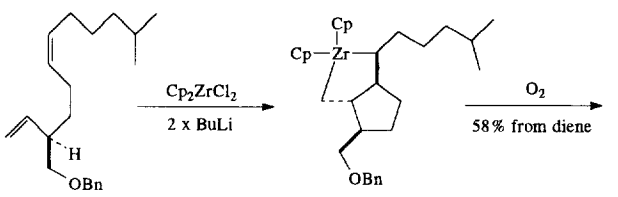


8 10 11

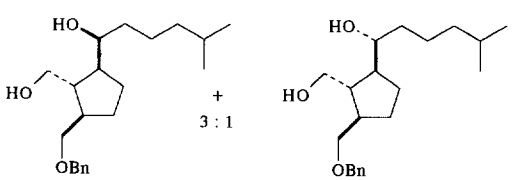
12 13

14 15

Scheme 1



15 2

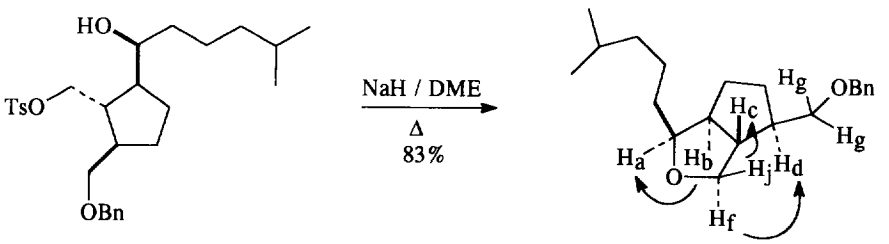


6 7

Scheme 2

Initially, the cyclozirconations were run in THF. However, the solvent was switched to toluene, as it was found that this helped to make product isolation easier. Yields and diastereomer ratios were the same for both solvents.

To establish the relative configuration of the two diastereomers, we prepared the monotosylates **16** and **17**. These diastereomers were now separable by column chromatography. The major diastereomer **16** was then converted into the cyclic ether **19** (NaH, DME, 80°C). This made the molecule rigid and allowed us to perform NOE[17] studies on it.

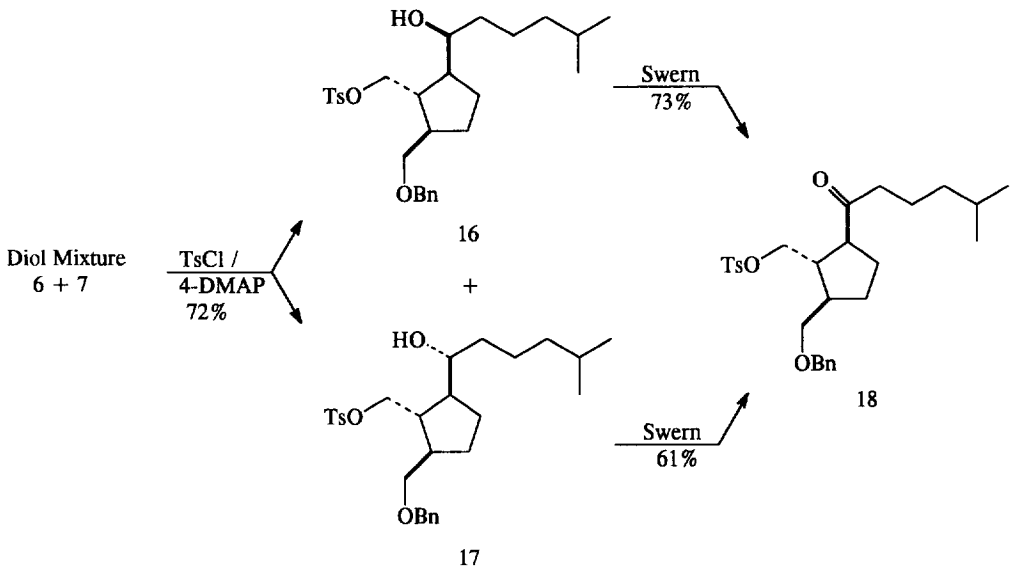


16 19

We confirmed our assignments of chemical shifts by running a 2D COSY NMR and a 2D ^{13}C-^{1}H correlated (HETCOR[18]) NMR on **19**. In the regular 1D ^{1}H NMR spectrum, three protons overlapped at ~3.5 ppm. From the 2D COSY,[19] we assigned them as H_f, H_g, and H_a. Careful examination of the 2D COSY (A/B cross peak) revealed that H_a was shifted by 0.04 ppm downfield from the multiplet (F/G on top of each other). Applying this knowledge to the NOE difference spectrum where H_b was irradiated, we observe a positive NOE enhancement of 8% at the chemical shift corresponding exclusively to H_a. Consequently, we can conclude that H_a and H_b are in fact on the same side. Therefore, cyclozirconation/ oxygenation must proceed with retention of alkene geometry in the major diastereomer.

The H_f and H_j methylene protons are diastereotopic, with H_j at a chemical shift at ~3.9 ppm and H_f at ~3.5 ppm. By irradiating H_j at 3.9 ppm, we observe a positive NOE for H_c of 4%. By irradiating H_f at 3.5 ppm, we observe a positive NOE for H_d. No NOE was observed between H_b and H_c. This establishes that H_b and H_c are on opposite faces of the molecule. The slow rate of cyclic ether formation (6 h, 80°C) confirms that the 5-5 ring fusion is trans.

To confirm the relative configuration of the minor diastereomer, the major and minor tosylates **16** and **17** were separately subjected to Swern oxidation (**Scheme 3**).[15] The resultant ketones **18** were found to be identical by TLC and ^{13}C NMR. This could only be possible if the monotosylates were identical in all respects except for the secondary alcohol center. Thus we can conclude with certainty that the minor tosylate is epimeric at that center and has structure **17**.



Scheme 3

We have observed that cyclozirconation of a diene having a substituent on the bridge connecting the two alkenes leads to a single predominant zirconacycle with control of three new stereogenic centers. Conversion of the C-Zr bonds to C-OH bonds, likely a free radical process (O_2 is a triplet species in the ground state), leads to some epimerization of the secondary carbon-zirconium bond (as expressed in the minor diol). Alternative methods of zirconacycle oxygenation are under further investigation in our laboratory.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were obtained on a Bruker AM-250 and/or WM-250 spectrometer as solutions in $CDCl_3$. Chemical shifts are reported in δ units downfield from the internal reference tetramethylsilane. The couplings (J) are reported in Hertz (Hz). Attached protons to carbon where determined using a spin-echo method of gated decoupling (JVERT).[20] This variation of the attached proton test gives positive signals (u) for carbons with an even number of protons attached (secondary or quaternary) and negative signals (d) for carbons with an odd number of protons attached (primary or tertiary). The infrared (IR) spectra were obtained neat and are reported in cm^{-1}. Substances for which C, H analysis are not reported were purified as specified and gave spectroscopic data consistent with being > 95% of the assigned structure. Organic chemicals were purchased from Aldrich Chemical Co. Zirconocene dichloride was stored and weighed out into flasks in a dry box. O_2 was passed through a six foot glass tube filled with drierite and activated 4 angstrom molecular sieves prior to introduction into cyclozirconations. THF and Et_2O were distilled from sodium/ benzophenone. Toluene and CH_2Cl_2 were

distilled from CaH_2. The solvent mixtures used for chromatography are volume/volume mixtures. R_f values indicated refer to thin layer chromatography on Analtech 2.5 x 10 cm 250 micron analytical plates coated with silica gel GF. Column chromatography was carried out with TLC-mesh silica gel, using the procedure we have described.[21] Unless otherwise specified, all reactions were carried out in flame-dried glassware under an atmosphere of N_2.

7-Methyl-2-(Z)-octen-1-ol (10). Following the method of Colonge,[9] Mg (15.115 g, 0.63 mol) and I_2 (a small crystal) were added to ether (500 mL). A portion of 1-bromo-3-methylbutane (5 mL) was added to the mechanically stirred reaction mixture until the I_2 color was gone. Then the remaining bromide (65.6 mL, 0.55 mol total) was added dropwise to the stirred mixture over 1 h so as to maintain a gentle reflux. The Grignard reagent **9** was chilled to 0°C before adding chloro alcohol[9] (26.5 g, 0.25 mol) over 25 min. The reaction mixture was warmed in a water bath (35 - 42°C) for an additional 1 h. It was then quenched by pouring the mixture over 10% aqueous HCl (273 mL) and ice. The resulting mixture was extracted with ether (3 x 100 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (30 mL), dried (Na_2SO_4), and concentrated. Fractional distillation of the crude oil through a 10 cm Vigreux column at 6 torr (bp 86-89°C) gave the allylic alcohol **10** (24.66 g, 69% yield) as a colorless oil, TLC R_f = 0.37 (20% EtOAc/ petroleum ether). A subsequent improvement in purification on large scale (200 g) was obtained via spinning band distillation at 5 torr (bp 84 - 85°C). ^{1}H NMR (δ): 5.70-5.49 (m, 2H), 4.20 (d, J = 5.6 Hz, 2H), 2.10-1.99 (m, 2H), 1.61-1.10 (m, 6H), 0.87 (d, J = 6.7 Hz, 6H); ^{13}C NMR (δ): u: 58.6, 38.5, 27.6, 27.4, d: 133.3, 128.3, 27.9, 22.6; IR (cm-1): 3319, 3015, 2955, 2829, 2869, 1468, 1384, 1366, 1022; MS (m/z,%): 124 (7), 111 (2), 109 (32); HRMS calc for $C_9H_{18}O$ 142.1358, obsd 142.1364.

10-Methyl-2-methylen-5-(Z)-undecen-1-ol (12). Following Trost,[10] a solution of n-chlorosuccinimide (20.0 g, 0.150 mol) in CH_2Cl_2 (300 mL) was chilled to 0°C. Methyl sulfide (16.8 mL, 0.229 mol) was added dropwise over 10 minutes. Allylic alcohol **10** (14.2 g, 0.100 mol) in CH_2Cl_2 (20 mL, 5M) was added dropwise over 10 minutes. The reaction was stirred for 2.5 h at 0°C before being diluted with water (100 mL). Layers were separated and the aqueous phase was extracted with CH_2Cl_2 (4 x 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was dissolved in petroleum ether and filtered through Florisil and concentrated. The crude oil was then vacuum filtered through a pad of coarse silica gel (50 g) with petroleum ether (3 x 50 mL). The first two fractions were concentrated to yield chloride (12.0 g, 75% yield) as a colorless oil, TLC R_f = 0.73 (5% EtOAc/petroleum ether). The intermediate chloride was carried forward without full characterization.

Following the method of Little,[8] TMEDA (8.7 mL, 57.6 mmol) was added dropwise over 5 minutes to n-BuLi (27.5 mL of a 2.1 M solution in hexane) at -78°C with solids precipitating. After stirring for 10 minutes, methallyl alcohol (2.9 mL, 34.5 mmol) was added dropwise over 5 minutes. The cooling bath was removed and stirring was continued for 19 h during which time the reaction became quite viscous. Subsequently, the reaction mixture was chilled to -78°C and the allylic chloride from above (2.32 g, 14.4

mmol) was added in petroleum ether (20 mL). The cooling bath was removed and the mixture was allowed to warm to room temperature with stirring for 1 h. The reaction was quenched by chilling with ice water bath and adding 10% aqueous HCl (30 mL). The mixture was extracted with ether (4 x 30 mL), dried (Na_2SO_4) and concentrated. The oily residue was chromatographed on silica gel (100 g). Elution with 6% EtOAc/petroleum ether and concentration gave the allylic alcohol **12** (1.85 g, 49% yield from alcohol **10**) as a colorless oil, TLC R_f = 0.23 (10% EtOAc/petroleum ether). Large scale (200 g) purification of this alcohol has been effected by spinning band distillation at 1 torr (bp 82 - 84°C). ^1H NMR (δ): 5.42-5.34 (m, 2H), 5.05 (s, 1H), 5.04 (s, 1H), 2.22-1.97 (m, 6H), 1.58-1.13 (m, 6H), 0.87 (d, J = 6.7 Hz, 6H); ^{13}C NMR (δ): u: 148.6, 109.5, 66.0, 38.6, 32.9, 27.5, 25.6, d: 130.6, 128.7, 27.9, 22.6; IR (cm^{-1}): 3329, 2954, 2927, 2869, 1468, 1384, 1366, 1067, 1024, 898; MS (m/z,%): 196 (18), 178 (12), 165 (46), 135 (22), 123 (33), 111 (29), 109 (34), 105 (11); HRMS calc for M + 1 $C_{13}H_{25}O$ 197.1905, obsd 197.1895.

(1R)-2-(Benzyloxymethyl)-2-(8-methyl-3-(Z)-nonenyl)-oxirane (13). The epoxidation was carried out using the catalytic Sharpless procedure.[11] L-(+)-Diethyl tartrate (0.19 mL, 1.11 mmol) and titanium tetraisopropoxide (0.28 mL, 0.94 mmol) were sequentially added to CH_2Cl_2 (10 mL) containing powdered 4Å molecular sieves (oven dried) at 0°C. This heterogenous mixture was stirred for 1 h at 0°C before cooling to -20°C. t-Butylhydroperoxide (7.4 mL of a 5M solution in CH_2Cl_2) was added and stirring was continued 10 minutes. Then allylic alcohol **12** (2.917 g, 14.86 mmol) was added dropwise in CH_2Cl_2 (15 mL). Stirring was continued for 12 h at -20°C. Subsequently, the reaction was warmed to 0°C and was quenched by the addition of H_2O (10 mL). After stirring for 15 minutes, 30% aqueous NaOH/saturated brine (5 mL) was added and stirring was continued for 60 minutes. The reaction mixture was filtered through celite with additional CH_2Cl_2 and then with H_2O (2 x 20 mL). The organic layer was separated and the aqueous portion was extracted with CH_2Cl_2 (2 x 40 mL), concentrated, and chromatographed on silica gel (100 g). Elution with 8% EtOAc/petroleum ether followed by concentration gave the epoxide (2.206 g, 70% yield) as a colorless oil, TLC R_f = 0.25 (20% EtOAc/petroleum ether). ^1H NMR (δ): 5.42-5.30 (m, 2H), 3.80 (d, J = 12.3 Hz, 1H), 3.65 (d, J = 12.3 Hz, 1H), 2.89 (d, J = 4.6 Hz, 1H), 2.70 (d, J = 4.6 Hz, 1H), 2.17-1.80 (m, 6H), 1.63-1.40 (m, 2H), 1.37-1.26 (m, 2H), 1.21-1.12 (m, 2H), 0.87 (d, J = 6.6 Hz, 6H); ^{13}C NMR (δ): u: 62.9, 59.5, 49.4, 38.6, 32.0, 27.44, 27.36, 22.4, d: 131.0, 128.2, 27.9, 22.6; IR (cm^{-1}): 3407, 3058, 2935, 2221, 1610, 1505, 1439, 1310, 1253, 1203, 1117, 1033, 1012; MS (m/z,%): 212 (2), 194 (3), 181 (5), 163 (15), 141 (9), 123 (31), 110 (46), 95 (71); HRMS calc for M + 1 $C_{13}H_{25}O_2$ 213.1854, obsd 213.1893.

By the method of Tanis,[22] a solution of epoxide (2.206 g, 10.39 mmol) in THF (20 mL) was added slowly to NaH (0.702 g, 17.6 mmol, 60% oil dispersion) in THF (30 mL). The reaction mixture was stirred for 10 minutes during which time it turned the color and consistency of pea soup. Benzyl bromide (1.3 mL, 10.39 mmol, caution: lachrymator) was added neat followed by $(Bu)_4NI$ (0.387 g, 1 05 mmol).

The mixture was stirred at room temperature for 5 h. Subsequently, the THF was removed by rotary evaporation. The residue was diluted with saturated aqueous NH_4Cl (40 mL) and extracted with ether (8 x 40 mL). The combined organic extracts were washed with brine (1 x 20 mL), dried (Na_2SO_4), and concentrated. The crude oil was chromatographed on silica gel (100 g). Elution with 4% EtOAc/ petroleum ether followed by concentration gave the benzyl-protected epoxide **13** (2.585 g, 82% yield) as a colorless oil, TLC R_f = 0.60 (10% EtOAc/petroleum ether). ^1H NMR (δ): 7.35-7.28 (m, 5H), 5.40-5.32 (m, 2H), 4.62-4.51 (AB multiplet, 2H), 3.63 (d, J = 11.1 Hz, 1H), 3.47 (d, J = 11.1 Hz, 1H), 2.73-2.67 (m, 2H), 2.14-1.87 (m, 5H), 1.68-1.49 (m, 2H), 1.36-1.13 (m, 4H), 0.86 (d, J = 6.7 Hz, 6H); ^{13}C NMR (δ): u: 138.0, 73.0, 72.0, 58.4, 50.4, 38.6, 32.0, 27.4, 22.5, d: 130.8, 128.5, 128.4, 127.7, 27.9, 22.6; IR (cm^{-1}): 3004, 2952, 2927, 2867, 1467, 1453, 1366, 1098; MS (m/z,%): 302 (3), 231 (21), 211 (11), 193 (12), 175 (22), 165 (21), 149 (13), 137 (19), 123 (31), 107 (74), 91 (100); HRMS calc for $C_{20}H_{30}O_2$ 302.2246, obsd 302.2249.

(2R)-2-(Benzyloxymethyl)-10-methyl-5-(Z)-undecen-1-ol (14). Following a modified Hutchins procedure,[12a] $NaBH_3CN$ (1.094 g, 17.4 mmol) was added to the benzyl-protected epoxide **13** (2.534 g, 8.38 mmol) in THF (28 mL). $BF_3 \cdot OEt_2$ (2.1 mL, 17.1 mmol) was added all at once. The reaction mixture was stirred for 3.5 h at room temperature. The reaction was quenched by the addition of brine (30 mL) and was allowed to stir (in the open air of the hood) overnight. This permitted complete decomposition of $NaBH_3CN$ (caution: HCN liberated on workup). The mixture was extracted with ether (5 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried (Na_2SO_4), and concentrated. The crude oil was chromatographed on silica gel (100 g). Elution with 8% EtOAc/petroleum ether gave the primary alcohol **14** (1.538 g, 60% yield) as a colorless oil, TLC R_f = 0.20 (10% EtOAc/petroleum ether). ^1H NMR (δ): 7.38-7.29 (m, 5H), 5.43-5.26 (m, 2H), 4.58-4.47 (AB multiplet, 2H), 3.74 (dd, J = 10.9, 3.4 Hz, 1H), 3.67-3.60 (m, 2H), 3.51-3.43 (m, 1H), 2.61 (bs, 1H), 2.10-1.84 (m, 5H), 1.63-1.44 (m, 1H), 1.42-1.26 (m, 4H), 1.23-1.11 (m, 2H), 0.86 (d, J = 6.6 Hz, 6H); ^{13}C NMR (δ): u: 138.0, 74.0, 73.5, 66.2, 38.6, 28.0, 27.4, 24.8, d: 130.6, 129.1, 128.5, 127.8, 127.6, 40.1, 27.9, 22.6; IR (cm^{-1}): 3421, 3003, 2953, 2926, 2867, 1467, 1454, 1365, 1093, 1028; MS (m/z,%): 304 (2), 213 (7), 195 (7), 177 (12), 135 (7), 123 (8), 121 (19), 109 (17), 107 (13), 95 (37), 91 (100); HRMS calc for $C_{20}H_{32}O_2$ 304.2402, obsd 304.2398.

(3R)-3-(Benzyloxymethyl)-11-methyl-dodeca-1,6-(Z)-diene (15). By analogy with Ireland's procedure for Swern oxidation,[15] DMSO (0.51 mL of a 7 M solution in CH_2Cl_2) was added dropwise to oxalyl chloride (0.24 mL of an 8 M solution in CH_2Cl_2) at -60°C. The mixture was stirred for 10 minutes before adding alcohol **14** (0.448 g, 1.47 mmol) in CH_2Cl_2 (11.3 mL). After stirring at -60°C for 50 minutes, triethylamine (1.1 mL, 7.9 mmol) was added and the reaction mixture was allowed to warm up to 0°C over 25 minutes. The crude mixture was then carried directly into the following ylide reaction without isolation. For the aldehyde: TLC R_f = 0.55 (10% EtOAc/petroleum ether).

Methylenetriphenyl phosphorane was generated by the slow addition of n-butyllithium (9.5 mL of a

2.2 M solution in hexane) to methyltriphenylphosphonium bromide (7.93 g, 22.2 mmol) in THF (44 mL) at -78°C. The reaction mixture turned lemon yellow initially and then a darker orange color. After stirring for 30 minutes, the crude aldehyde reaction mixture from above was added slowly. This was followed by a THF flask rinse (2 x 9 mL). Stirring was continued overnight (ice bath slowly melts). The reaction was quenched by the addition of 10% aqueous HCl (30 mL) and was extracted with ether (3 x 40 mL). Each extract was washed with the same portion of brine (30 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and chromatographed on silica gel (10 g). Elution with 1% EtOAc/petroleum ether gave the diene **15** (0.310 g, 70% yield from alcohol **14**) as a colorless oil, TLC R_f = 0.38 (5% EtOAc/ petroleum ether). ^1H NMR (δ): 7.38-7.25 (m, 5H), 5.75-5.60 (m, 1H), 5.41-5.29 (m, 2H), 5.11-5.07 (m, 1H), 5.06-5.03 (m, 1H), 4.51 (s, 2H), 3.39 (d, J = 6.4 Hz, 2H), 2.41-1.93 (m, 1H), 2.41-1.93 (m, 4H), 1.63-1.47 (m, 2H), 1.39-1.24 (m, 3H), 1.22-1.11 (m, 2H), 0.86 (d, J = 6.6 Hz, 6H); ^{13}C NMR (δ): u: 130.6, 115.7, 73.8, 73.0, 38.7, 31.3, 27.5, 24.6, d: 140.1, 130.3, 129.4, 128.3, 127.5, 127.4, 43.7, 27.9, 22.6; IR (cm^{-1}): 2954, 2926, 2855, 1454, 1353, 1103, 913; MS (m/z,%): 301 (1), 300 (3), 209 (3), 191 (3), 173 (6), 135 (6), 121 (6), 109 (9), 107 (8), 95 (11), 91 (100); HRMS calc for $C_{21}H_{32}O$ 301.2531, obsd 301.2460.

(1S,2R,3R)-3-(Benzyloxymethyl)-2-(hydroxymethyl)-1-[5-methyl-(1S)-hydroxyhexyl]-cyclopentane (6) and (1S,2R,3R)-3-(Benzyloxymethyl)-2-(hydroxymethyl)-1-[5-methyl-(1R)-hydroxyhexyl] cyclopentane (7). n-Butyllithium (0.76 mL of a 2.2 M solution in hexane) was added to zirconocene dichloride (0.247 g, 0.84 mmol) and diene **15** (0.210 g, 0.70 mmol) in toluene (2.2 mL) at -5°C. After stirring for 10 minutes, the cooling bath was removed and the mixture was permitted to warm to room temperature. Stirring was continued for 14 h during which time the reaction mixture turned a reddish-brown color. The mixture was then chilled to 0°C and a stream of O_2 was bubbled through the stirred reaction mixture for 6 minutes. During this time the reaction lightened in color. A mixture of $NaBH_4$ (0.082 g, 2.18 mmol) in 95% ethanol (1 mL) was added and stirring was continued for 15 minutes to break up the solids formed during oxygenation. The reaction was carefully quenched by pouring it into a 1:1 solution of 5% H_2SO_4/ saturated aqueous Na_2SO_4 (20 mL), and ether (25 mL). The layers were separated and the aqueous layer was extracted with additional ether (7 x 10 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and chromatographed on silica gel (10 g). Elution with 40% EtOAc/petroleum ether gave the diols **6** and **7** as a 3:1 mixture (0.135 g, 58% yield) as a colorless oil, TLC R_f = 0.48 (40% EtOAc/ petroleum ether). ^1H NMR (δ): 7.38-7.26 (m, 5H), 4.51 (s, 2H), 3.71-3.65 (m, 1H), 3.59-3.28 (m, 5H), 1.89-1.86 (m, 1H), 1.70-1.60 (m, 4H), 1.58-1.16 (m, 10H), 0.87 (d, J = 6.6 Hz, 6H); ^{13}C NMR (δ): (major diol **6**) u: 138.2, 74.0, 73.0, 66.4, 39.0, 36.2, 29.0, 28.2, 23.0, d: 128.3, 127.5, 75.5, 52.1, 50.3, 43.4, 27.8, 22.6, 22.4, (minor diol **7**) u: 137.6, 74.2, 73.2, 66.1, 38.9, 35.0, 28.3, 24.9, 24.2, d: 128.4, 127.7, 71.7, 49.6, 48.4, 44.8, 27.8, 22.6, 22.4; IR (cm^{-1}): 3315, 2951, 2933, 2867, 1454, 1353, 1089, 1075, 1028; MS (m/z,%): 316 (5), 249 (9), 225 (8), 207 (6), 192 (12), 179 (9), 141 (7), 111 (18), 107 (18), 95 (24), 91

(100); HRMS calc for $C_{21}H_{34}O_3$ 334.2508, obsd 334.2448.

(1S,2R,3R)-3-(Benzyloxymethyl)-1-[5-methyl-(1S)-hydroxyhexyl]-2-(tosyloxymethyl) cyclopentane (16) and (1S,2R,3R)-3-(Benzyloxymethyl)-1-[5-methyl-(1R)-hydroxyhexyl]-2-(tosyloxymethyl)-cyclopentane (17). The mixture of diols **6** and **7** (0.180 g, 0.32 mmol) was dissolved in CH_2Cl_2 (1.6 mL) and chilled to 0°C. 4-DMAP (0.068 g, 0.56 mmol) was added. p-Toluenesulfonyl chloride (0.070 g, 0.37 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and was added dropwise in 3 portions over 45 minutes.[23] After stirring at 0°C for 3.5 h, the reaction mixture was poured into 5% aqueous HCl (10 mL) and extracted with ether (3 x 25 mL). Each extract was washed with the same portion of brine (10 mL). The combined extracts were dried (Na_2SO_4) and chromatographed on silica gel (5 g). Elution with 10% EtOAc/petroleum ether followed by concentration gave the major tosylate **16** (0.090g, 57% yield) as a colorless oil, TLC R_f = 0.40 (20% EtOAc/ petroleum ether). ^{1}H NMR (δ): 7.77 (d, J = 8.1 Hz, 2H), 7.36-7.26 (m, 7H), 4.44 (s, 2H), 4.14 (d, J = 5.2 Hz, 2H), 3.34 (d, J = 6.2 Hz, 3H), 2.42 (s, 3H), 2.12-2.05 (m, 1H), 1.98-1.93 (m, 1H), 1.75-1.10 (m, 13H), 0.87 (d, J = 6.6 Hz, 6H); ^{13}C NMR (δ): u: 144.5, 138.5, 133.3, 73.9, 73.4, 72.9, 38.9, 36.4, 28.8, 28.6, 23.3, d: 129.7, 128.3, 127.9, 127.4, 75.9, 48.0, 44.9, 42.5, 27.9, 22.6, 22.5, 21.5, IR (cm^{-1}): 3549, 2951, 2932, 2867, 1454, 1383, 1360, 1189, 1176, 1097, 938, 814, MS (m/z,%): 231 (25), 192 (11), 172 (17), 139 (11), 111 (12), 107 (21), 91 (100); HRMS calc for $C_{28}H_{40}SO_5$ 488.2596, obsd 488.2511. Elution with 15% EtOAc/petroleum ether and concentration gave the minor tosylate **17** (0.023 g, 15% yield) as a colorless oil, TLC R_f = 0.28 (20% EtOAc/ petroleum ether). ^{1}H NMR (δ): 7.76 (d, J = 8.2 Hz, 2H), 7.35-7.25 (m, 7H), 4.42 (s, 2H), 4.14-4.00 (m, 2H), 3.59-3.51 (m, 1H), 3.34 (d, J = 6.0 Hz, 2H), 2.41 (s, 3H), 1.99-1.13 (m, 15H), 0.87 (d, J = 6.6 Hz, 6H); ^{13}C NMR (δ): u: 144.5, 138.4, 133.1, 73.4, 72.9, 72.6, 38.9, 36.2, 28.3, 24.3, 23.9, d: 129.7, 128.2, 127.8, 127.4, 71.8, 47.9, 43.7, 41.8, 27.8, 22.5, 21.5, IR (cm^{-1}): 3442, 2952, 2932, 2867, 1598, 1496, 1454, 1363, 1189, 1177, 1097, 937, 814; (m/z,%): 231 (3), 207 (6), 192 (10), 172 (6), 139 (5), 121 (6), 111 (9), 108 (12), 107 (6), 95 (21), 91 (100); HRMS calc for $C_{28}H_{40}SO_5$ 488.2596, obsd 488.2585.

(1S,2S,3R,4R)-4-(Benzyloxymethyl)-1-(4-methylpentyl)-hexahydro-cyclopenta[c]furan (19). A solution of alcohol **16** (0.136 g, 0.278 mmol) in DME (3.0 mL) was added to a 5 mL reactivial. NaH (0.064 g, 1.60 mmol, 60% oil dispersion) was added carefully to control gas evolution. The vial was sealed and heated with stirring at 80°C for 6 h. The reaction was carefully diluted with saturated aqueous NH_4Cl (20 mL) and extracted with 20% EtOAc/petroleum ether (4 x 25 mL). The combined organics were dried (Na_2SO_4), concentrated, and chromatographed on silica gel (5 g). Elution with 4% EtOAc/petroleum ether gave the cyclic ether **19** (0.074 g, 83% yield) as a colorless oil. TLC R_f = 0.49 (10% EtOAc/petroleum ether). ^{1}H NMR (δ): 7.37-7.27 (m, 5H), 4.50-4.44 (AB multiplet, 2H), 3.94-3.88 (m, 1H), 3.53-3.43 (m, 3H), 3,32-3.26 (m, 1H), 2.33-2.28 (m, 1H), 2.12-2.03 (m, 2H), 1.91-1.74 (m, 2H), 1.72-1.13 (m, 10H), 0.86 (d, J = 6.6 Hz, 5H); ^{13}C NMR (δ): u: 138.6, 74.3, 73.0, 68.0, 39.1, 35.4, 34.2, 23.8, 23.5, d: 128.3, 127.5, 127.4, 79.4, 58.6, 58.4, 38.7, 27.9, 22.6, 22.5; IR (cm^{-1}): 2953, 2931, 2867, 1466, 1453, 1364, 1112, 1096,

970, 892; MS (m/z,%): 316 (2), 231 (53), 207 (5), 181 (32), 180 (30), 165 (5), 139 (21), 111 (9), 107 (11), 95 (14), 91 (100); HRMS calc for $C_{21}H_{32}O_2$ 316.2402, obsd 316.2371.

3-(Benzyloxymethyl)-2-(hydroxymethyl)-1-(5-methyl-hexan-1-one) cyclopentane (18). DMSO (0.36 mL of a 7M solution in CH_2Cl_2) was added dropwise to oxalyl chloride (0.19 mL of an 8 M solution in CH_2Cl_2) at -60°C.[15] The mixture was stirred for 10 minutes before adding the alcohol **16** (0.104 g, 0.213 mmol) in CH_2Cl_2 (2.0 mL). After stirring at -60°C for 1 h 15 minutes, triethylamine (0.74 mL, 5.31 mmol) was added and the reaction mixture was allowed to warm to -20°C. After 30 minutes the reaction mixture was diluted with brine (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with a second brine portion (20 mL), dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (10 g) with 8% EtOAc/petroleum ether and concentrated to yield the ketone **18** (0.075 g, 73% yield) as an amber oil, TLC R_f = 0.45 (20% EtOAc/ petroleum ether). ^{1}H NMR (δ): 7.74 (d, J = 6.7 Hz, 2H), 7.36-7.22 (m, 7H), 4.42 (s, 2H), 4.10 (dd, J = 9.6, 4.2 Hz, 1H), 3.99 (dd, J = 9.6, 6.1 Hz, 1H), 3.41-3.28 (m, 2H), 2.90-2.80 (m, 1H), 2.42 (s, 3H), 2.39-2.30 (m, 3H), 2.08-1.40 (m, 8H), 1.16-1.07 (m, 2H), 0.87 (d, J = 6.6 Hz, 6H); ^{13}C NMR (δ): u: 211.9, 144.6, 138.3, 133.0, 73.2, 73.0, 72.0, 42.4, 38.4, 29.1, 28.6, 21.4, d: 129.8, 128.3, 127.8, 127.43, 127.35, 53.9, 44.2, 41.4, 27.8, 22.4, 21.5; IR (cm^{-1}): 2953, 2868, 1708, 1600, 1453, 1363, 1189, 1177, 1097, 957, 815; MS (m/z,%): 486 (7), 395 (11), 379 (14), 314 (13), 257 (18), 223 (31), 208 (17), 172 (15), 159 (12), 138 (32), 123 (17), 113 (52), 111 (18), 107 (28), 95 (86), 91 (100); HRMS calc for $C_{28}H_{38}SO_5$ 486.2440, obsd 486.2450.

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