Title: One-pot synthesis of 3,4-disubstituted 2-methylcyclopent-2-enols as useful building blocks

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General methods

$^1$H NMR spectra were recorded either on a Bruker DPX 250 (250 MHz), DRX-300 (300 MHz) or AV-360 (360 MHz) instrument and coupling constants ($J$) are reported in Hz to ± 0.5 Hz. The following abbreviations were utilized to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet and m = multiplet, app = apparent. Molecular sieves and K$_2$CO$_3$ were added to stock deuterchloroform. Chemical shifts are quoted in parts per million (ppm) and are referenced to residual H signal of deuterchloroform (7.26 ppm). $^{13}$C NMR chemical shift are expressed in parts per million (ppm), reported from the central peak of deuterchloroform (77.36 ppm). When measured, DEPT signals are referred as (+) or (−) following the corresponding signals. Infrared spectra were recorded as solutions in CH$_2$Cl$_2$ using NaCl salt plates (thin film), on a Perkin-Elmer Spectrum One FT-IR. Absorption maxima ($\nu$) are reported in wavenumbers (cm$^{-1}$). High-resolution mass spectra ($m/z$) were obtained by direct introduction (ESI) on a TSQ (Thermo Scientific. 2009) mass spectrometer with direct introduction and only molecular species [M + Na]$^+$ are reported. The quoted masses are accurate to ± 5 ppm. X-Ray analysis was carried out using a Kappa X8 APPEX II Bruker diffractometer with graphite-monochromated MoK$\alpha$ radiation ($\lambda = 0.71073$ Å). The temperature of the crystal was maintained at the selected value (100 K) by means of a 700 series Cryostream cooling device to within an accuracy of ±1 K. The data were corrected for Lorentz polarization and absorption effects. The structures were solved by direct methods using SHELXS-97 and refined against F2 by full-matrix least-squares techniques using SHELXL-97 with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were located on a difference Fourier map and introduced into the calculations as a riding model with isotropic thermal parameters. All calculations were performed by using the Crystal Structure crystallographic software package WINGX.

Flash chromatography was performed on silica gel Merck Geduran Si60 (63-200 µm) or Chromagel Si60ACC (70-200) pH = 7 for acid sensitive products) as the stationary phase. Analytical TLC was performed on glass plates pre-coated with silica gel (Merck silica gel, 60 F254), which were visualized with UV fluorescence when applicable ($\lambda_{max} = 254$ nm) and/or by staining with vanillin or p-anisaldehyde ethanolic sulphuric acid solutions followed by heating. Tetrahydrofuran (THF) and diethyl ether (Et$_2$O) were distilled from sodium/benzophenone and dichloromethane (CH$_2$Cl$_2$) from CaH$_2$. All air and/or water sensitive reactions were carried out under a nitrogen atmosphere using a dual manifold high vacuum line with dry, freshly distilled solvents using standard syringe-cannula/septa and purge-and-refill techniques. All glassware was dried with flameless heat gun and under vacuum before operating.

(±)-Di-tert-butyl 3-methyl-4-oxocyclopent-2-ene-1,2-dicarboxylate (9)

See text (Reference Section) for preparative scale.

Pale yellow oil; $R_f = 0.49$ (Hept/EtOAc 3:1). IR: $\nu = 2980$, 1720, 1457, 1369, 1337, 1248, 1155, 1075 cm$^{-1}$.

$^1$H NMR (250 MHz, CDCl$_3$): $\delta = 3.81$ (br d, $J = 7.7$, 1H), 2.73 (dd, $J = 19.1$, 7.7 Hz, 1H), 2.45 (dd, $J = 19.1$, 1H), 2.45 (dd, $J = 19.1$, 1H), 2.45 (dd, $J = 19.1$, 1H).
2.7 Hz, 1H), 2.05 (d, J = 1.9 Hz, 3H), 1.53 (s, 9H), 1.43 (s, 9H) ppm. $^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta$ = 207.6, 171.5, 163.9, 154.1, 147.5, 82.8, 81.9, 45.3, 38.7, 28.3 (3 C), 28.0 (3 C), 10.0 ppm. HRMS -ESI: m/z [M + Na]$^+$ calcld for C$_{16}$H$_{26}$O$_5$ + Na: 319.1521; found: 319.1511.

These data are in agreement with those reported by Yavari et al.$^1$

(±)-Di-tert-butyl 4-hydroxy-3-methylcyclopent-2-ene-1,2-dicarboxylate (cis-10 and trans-10)

![Di-tert-butyl 4-hydroxy-3-methylcyclopent-2-ene-1,2-dicarboxylate](image)

To a solution of cyclopentenone 9 (16.4 g, 55.4 mmol, 1 equiv.) in dry MeOH (50 mL) at –50 °C was added NaBH$_4$ (2.30 g, 60.9 mmol, 1.1 equiv.). The reaction mixture was stirred at the same temperature overnight, then added with brine and extracted with EtOAc (x3). The combined organic layers were dried with MgSO$_4$ and the solvent was removed under reduced pressure. The crude product (95:5 mixture of cis/trans isomers from crude $^1$HNMR) was purified by flash column chromatography (Hept/EtOAc, 1:0 up to 1:1) to give in order of elution the pure major isomer cis-10 (13.5 g, 82%) and the corresponding minor isomer trans-10 (0.29 g, 2.1%).

cis-10

R$_f$ = 0.27 (Hept/EtOAc 3:1). IR: $\nu$ = 3371, 2980, 1715, 1458, 1369, 1258, 1160, 1046 cm$^{-1}$. $^1$H NMR (360 MHz, CDCl$_3$): $\delta$ = 4.42 (br d, J = 11.4, 6.8 Hz, 1H), 3.53 (br d, J = 8.6, 1H), 3.04 (d, J = 11.4 Hz, 1H), 2.27 (ddd, J = 14.5, 8.2, 6.8 Hz, 1H), 2.21 (d, J = 1.8 Hz, 3H), 1.79 (ddd, J = 14.1, 1.6, 1.6 Hz, 1H), 1.50 (s, 9H), 1.47 (s, 9H). $^{13}$C NMR (90.6 MHz, CDCl$_3$): $\delta$ = 176.3, 164.7, 157.4, 130.3, 81.8, 81.2, 81.0, 51.1, 36.5, 28.5 (3 C), 28.3 (3 C), 14.2. HRMS-ESI: m/z [M + Na]$^+$ calcld for C$_{16}$H$_{26}$O$_5$ + Na: 321.1678; found: 321.1680.

trans-10

R$_f$ 0.20 (Hept/EtOAc 3:1). $^1$H NMR (360 MHz, CDCl$_3$): $\delta$ = 4.76 (br dd, J = 5.9, 5.5 Hz, 1H), 3.67 (ddq, J = 9.5, 1.5, 1.5 Hz, 1H), 2.52 (d, J = 6.4 Hz, 1H), 2.27 (ddd, J = 13.6, 7.7, 3.2 Hz, 1H), 2.10 (br s, 3H), 1.91 (ddd, J = 13.6, 9.5, 5.9 Hz, 1H), 1.45 (s, 9H), 1.39 (s, 3H). $^{13}$C NMR (90.6 MHz, CDCl$_3$): $\delta$ = 174.2, 164.8, 156.7, 129.6, 81.0, 80.8, 80.3, 50.5, 37.5, 28.5, 28.3, 13.5 ppm. HRMS-ESI: m/z [M + Na]$^+$ calcld for C$_{16}$H$_{26}$O$_5$ + Na: 321.1678; found: 321.1663.

(±)-cis-tert-Butyl 5-formyl-3-hydroxy-2-methylcyclopent-1-enecarboxylate (11); (±)-cis-tert-Butyl 3-hydroxy-5-(hydroxymethyl)-2-methylcyclopent-1-enecarboxylate (12)

![Di-tert-butyl 5-formyl-3-hydroxy-2-methylcyclopent-1-enecarboxylate](image) and ![Di-tert-butyl 3-hydroxy-5-(hydroxymethyl)-2-methylcyclopent-1-enecarboxylate](image)

A solution of diester cis-10 (108 mg, 0.36 mmol, 1 equiv.) in CH$_2$Cl$_2$ (4 mL) was cooled to –78 °C and a 1M solution of DIBAL in toluene (0.76 mL, 0.76 mmol, 2.1 equiv.) was added dropwise. The reaction mixture
was stirred at the same temperature for 5 h and quenched with saturated aqueous solution of Rochelle’s salt, then extracted with CH₂Cl₂ (x3). The combined organic layers were washed with brine and dried over MgSO₄, filtered over Celite®/Silica and washed with Et₂O / Pentane (1:1). The solvents were removed under reduced pressure and the residue submitted to flash column chromatography (Hept/EtOAc, 1:0 up to 1:1) to give the desired aldehyde 11 (33 mg, 40%, yellow oil) as well as the corresponding alcohol 12 (18 mg, 22%).

The alcohol 12 was oxidized as following: To a solution of diol 12 (85 mg, 0.37 mmol, 1 equiv.) in CH₂Cl₂ (4 mL) were added TEMPO (11 mg, 0.07 mmol, 0.2 equiv.) and BIAB (131 mg, 0.41 mmol, 1.1 equiv.). The reaction mixture was stirred at the same temperature overnight and quenched with saturated aqueous solution of Na₂S₂O₃ and extracted with CH₂Cl₂ (x3). The combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (Hept/EtOAc, 1:0 up to 1:1) to give pure aldehyde 11 (63 mg, 75%). This hydroxylaldehyde proved particularly labile and had to be used as soon as purified.

**Aldehyde 11** (major adduct)

RF 0.30 (Hept/EtOAc 1:1); IR: ν = 3372.4, 3050.3, 2976.0, 2906.2, 2828.2, 1720.3, 1616.7, 1465.1, 1372.2, 1348.5, 1255.1, 1162.3 cm⁻¹. ¹H NMR (360 MHz, CDCl₃): δ = 9.87 (d, 1H, J = 2.3 Hz), 4.53 dd, 1H, J = 7.0, 3.4 Hz), 3.78 (m, 1H), 2.63 (br s, 1H, OH), 2.26 (ddd, 1H, J = 14.3, 8.0, 7.4)), 2.15 (br d, 3H, J = 1.8 Hz), 1.80 (dt app, 1H, J = 14.1, 3.9, 3.7 Hz), 1.48 (s, 9H). ¹³C NMR (CDCl₃, 75.4 MHz): δ = 203.5, 164.6, 157.8, 129.2, 82.0, 80.4, 56.2, 33.4, 28.5 (3 C), 14.0. HRMS (ESI): m/z [M + Na]⁺ calcd for C₁₂H₁₉O₄ (M + Na)⁺ 249.1102; found 249.1097.

**Alcohol 12**

¹H NMR (360 MHz, CDCl₃): δ = 4.33 (d, 1H, J = 6.6 Hz), 3.94 (dd, 1H, J = 10.4, 2.2 Hz), 3.59 (dd, 1H, J = 10.4, 3.2 Hz), 3.03 (ddd, 1H, J = 6.5, 2.8, 1.4 Hz), 2.60 (br s, 1H, OH), 2.33 (ddd, 1H, J = 14.2, 8.8, 7.2 Hz), 2.11 (d, 3H, J = 1.3 Hz), 1.75 (br s, 1H, OH), 1.57 (dt, 1H, J = 14.2, 1.5 Hz), 1.50 (s, 9H). ¹³C NMR (CDCl₃, 62.9 MHz): δ = 166.1, 155.7, 130.6, 81.2, 79.8, 63.5, 47.0, 36.6, 28.6 (3 C), 14.6. HRMS (ESI): m/z [M + Na]⁺ calcd for C₁₂H₂₀O₄ (M + Na)⁺ 251.1259, found 251.1252.

(±)-**cis-tert-Butyl 3-hydroxy-2-methyl-5-vinylcyclopent-1-enecarboxylate (13)**

![Diagram](image-url)

To solution of Ph₃PCH₂Br (157 mg, 0.44 mmol, 4 equiv.) in THF (1 mL) at −78 °C was added a 2.1 M solution of BuLi (0.20 mL, 0.43 mmol, 3.9 equiv.). The reaction was stirred at the same temperature for 30 min until total dissolution of the solid. A solution of aldehyde 11 (25 mg, 0.11 mmol, 1 equiv.) in THF (1 mL) was added dropwise. The reaction mixture was stirred and allowed to warm up to 0 °C for 2 h, then quenched with saturated aqueous NaHCO₃ and extracted with Et₂O (x3). The combined organic layers were washed with brine and dried over MgSO₄ and filtered. The solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (Hept/EtOAc, 1:0 up to 1:1) to give diene
13 as a colorless oil (6 mg, 27%). Rf 0.45 (Hept/EtOAc 1:1). IR: ν = 3372.4, 3050.3, 2953.1, 2906.2, 2883.4, 1709.7, 1616.7, 1430.1, 1348.5, 1255.1, 1162.3 cm\(^{-1}\). \(^1\)H NMR (360 MHz, CDCl\(_3\)): δ = 5.87 (ddd, 1H, J = 17.7, 10.2, 7.7 Hz), 5.05 (dt, 1H, J = 17.3, 1.4 Hz), 5.00 (br d, 1H, J = 10.0 Hz), 4.51 (br t, 1H, J = 5.7 Hz), 3.41 (br q, 1H, J = 6.4 Hz), 2.49 (dt, 1H, J = 14.1, 7.7 Hz), 2.09 (br d, 3H, J = 1.4 Hz), 1.53 (dt, 1H, J = 14.1, 7.7 Hz), 1.48 (s, 9H). \(^13\)C NMR (CDCl\(_3\), 62.9 MHz): δ = 164.3, 155.1, 141.7, 133.6, 114.0, 80.6, 80.2, 47.2, 38.8, 28.2 (3 C), 13.5. HRMS-ESI: m/z [M + Na]\(^+\) calcld for C\(_{13}\)H\(_{28}\)O\(_3\) + Na: 247.1309, found 247.1306.

\((\pm)-\text{cis-}\text{tert-Butyl 5-acetyl-3-hydroxy-2-methylcyclopent-1-enecarboxylate (14)}\)

\[\text{HO} \quad \text{CO}_2\text{t-Bu} \]

To a solution of PdCl\(_2\) (1.6 mg, 0.009 mmol, 0.1 equiv.) in DMF/H\(_2\)O (0.3 mL/0.1 mL) at rt was added CuCl (9.7 mg, 0.098 mmol, 1.1 equiv.). The reaction was stirred at the same temperature for 1h under an atmosphere of O\(_2\) (balloon). Olefin 13 (20 mg, 0.089 mmol, 1 equiv.) was added and the reaction was stirred at rt overnight then quenched with a saturated aqueous NH\(_4\)Cl and extracted with Et\(_2\)O (x3). The combined organic layers were washed with brine (x5), dried with MgSO\(_4\) and filtered. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on neutral silica (Hept / EtOAc, 1:0 up to 1:1), to give pure 14 as a yellow oil (15 mg, 70%). **This hydroxyketone proved rather labile and could not be stored without decomposition.** Rf 0.25 (Hept/EtOAc 1:1). IR: ν = 3370.7, 2990.0, 2906.9, 1721.0, 1716.7, 1616.1, 1464.9, 1372.2, 1348.5, 1255.1, 1162.3 cm\(^{-1}\). \(^1\)H NMR (360 MHz, CDCl\(_3\)): δ = 4.44 (br t, 1H, J = 7.1 Hz), 3.91 (br d, 1H, J = 8.2 Hz), 3.09 (d, 1H, J = 10.0 Hz, OH), 2.39 (s, 3H), 2.21 (ddd, 1H, J = 13.9, 6.5, 4.6 Hz), 2.18 (d, 3H, J = 1.4 Hz), 1.66 (ddd, 1H, J = 14.5, 1.8, 1.6 Hz), 1.49 (s, 9H). \(^13\)C NMR (CDCl\(_3\), 90.6 MHz): δ = 211.8, 164.4, 158.5, 128.6, 79.8, 56.0, 51.3, 35.9, 29.5, 14.2. HRMS-ESI: m/z [M + Na]\(^+\) calcld for C\(_{13}\)H\(_{28}\)O\(_3\) + Na: 263.1259, found 263.1261.

\((\pm)-\text{cis-Dimethyl 4-hydroxy-3-methylcyclopent-2-ene-1,2-dicarboxylate (15)}\)

\[\text{HO} \quad \text{CO}_2\text{Me} \quad \text{CO}_2\text{Me} \]

The di-\textit{tert-}butyl hydroxydiester cis-10 (13.5 g, 45.3 mmol, 1 equiv.) was diluted in dry CH\(_2\)Cl\(_2\) (100 mL) and added with trifluoroacetic acid (3.47 mL, 453.0 mmol, 10 equiv.). The reaction mixture was stirred at rt for 3 h, then TFA and the solvent were removed under reduced pressure. The crude hydroxydiacid (white solid) was added with dry MeOH/Et\(_2\)O (1:3, 120 mL) and a 1M solution of TMSCHN\(_2\) in Et\(_2\)O (95 mL, 2.1 equiv.) was added. The reaction mixture was stirred for 2 h at rt and the excess of TMSCHN\(_2\) and solvents were removed under reduced pressure. The residue was purified by flash column chromatography (Hept / EtOAc, 1:0 up to 1:1) to give dimethyl ester 15 as a yellow oil (7.75 g, 80%). Rf 0.29 (Hept/EtOAc 1:1). IR: ν = 3424, 2954, 1720, 1437, 1351, 1275, 1219, 1174, 1048 cm\(^{-1}\). \(^1\)H NMR (360 MHz, CDCl\(_3\)): δ = 4.49
(br d, $J = 5.4$ Hz, 1H), 3.72 (s, 6H), 3.65 (br d, $J = 6.9$ Hz, 1H), 3.02 (br s, 1H, OH), 2.40 (ddd, 14.5, 8.6, 7.3, 1H), 2.20 (d, $J = 1.4$ Hz, 3H), 1.81 (ddd, 1H, $J = 14.5, 3.0, 2.5$ Hz, 1H). $^{13}$C NMR (90.6 MHz, CDCl$_3$): $\delta = 177.1, 165.7, 159.0, 128.2, 80.6, 52.9, 51.8, 49.2, 36.6, 14.2$. HRMS-ESI: $m/z$ [M + Na]$^+$ calcd for C$_{10}$H$_{14}$O$_5$ + Na: 237.0739; found 237.0733.

(±)-cis-Methyl 3-hydroxy-5-[methoxy(methyl) carbamoyl]-2-methylcyclopent-1-enecarboxylate (16)

See Reference Section.

(±)-cis-Methyl 3-hydroxy-5-(isopropylcarbamoyl)-2-methylcyclopent-1-enecarboxylate (17)

A 2 M solution of trimethylaluminum in toluene (0.47 mL, 0.94 mmol, 2 equiv.) was added dropwise at 0 °C to dry isopropylamine (0.08 ml, 0.94 mmol, 2 equiv.) in CH$_2$Cl$_2$ (5 mL). To this solution at −15 °C was added a solution of dimethyl ester 15 (100 mg, 0.47 mmol, 1 equiv.) in CH$_2$Cl$_2$ (5 mL). The reaction mixture was stirred at this temperature for 1 h, then 3 h at rt before addition of a saturated solution of Rochelle’s salt followed by extraction with Et$_2$O (x 5). The combined organic layers were washed with brine, dried with MgSO$_4$ and filtered. The solvent was removed in vacuo and the crude product (108 mg) purified by flash column chromatography (Hept/EtOAc, 1:0 up to 1:3) to give pure amide 17 as a yellow oil (83 mg, 74%). R$_f$ 0.15 (Hept/EtOAc 1:1). IR: $\nu = 3253, 2949, 1722, 1658, 1435, 1274, 1220, 1111, 1046$ cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 6.20$ (d, 1H, $J = 7.5$ Hz), 4.78 (d, 1H, $J = 11.3$ Hz), 4.34 (dd, 1H, $J = 6.4$; 10.9 Hz), 3.95 (m, 1H), 3.69 (s, 3H), 3.46 (br d, 1H, $J = 7.4$ Hz), 2.16 (s, 3H), 2.07 (dt, 1H, $J = 14.1, 7.2$ Hz), 1.87 (d, 1H, $J = 14.0$ Hz), 1.11 (d, 3H, $J = 6.4$ Hz), 1.07 (d, 3H, $J = 6.4$ Hz). $^{13}$C NMR (75.4 MHz, CDCl$_3$, DEPT): $\delta = 174.0, 166.3, 159.5, 128.1, 80.6, 52.3, 51.6, 42.2, 35.9, 22.8, 22.6, 14.8$. HRMS-ESI: $m/z$ [M + Na]$^+$ calcd for C$_{12}$H$_{18}$NO$_4$ + Na: 264.1212, found 264.1229.

(±)-cis-Methyl 5-acetyl-3-hydroxy-2-methylcyclopent-1-enecarboxylate (18)

Procedure A (from Weinreb amide 16): A solution of Weinreb amide 16 (6.78 g, 27.9 mmol, 1 equiv.) in THF (100 mL) was cooled to 0 °C and a 3 M ethyl ether solution of MeMgBr (23.3 mL, 69.8 mmol, 2.5 equiv.) was added dropwise. The reaction mixture was stirred at the same temperature for 30 min, then
quenched with saturated aqueous NH₄Cl and extracted with EtOAc (x3). The combined organic layers were washed with brine, dried with MgSO₄ and filtered. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (Hept/EtOAc, 1:0 up to 1:1). Pure methylketone 18 was obtained as a yellow oil (828 mg, 15%, 35% based on recovered starting material). Rₐ 0.20 (Hept/EtOAc 1:1). IR: v = 3372.4, 2986.0, 2906.2, 1720.3, 1716.5, 1616.7, 1465.1, 1372.2, 1348.5, 1255.1, 1162.3 cm⁻¹. ¹H NMR (250 MHz, CDCl₃): δ = 4.45 (dd, 1H, J = 9.5, 7.8 Hz), 3.93 (br d, 1H, J = 8.2 Hz), 3.72 (s, 3H, CH₃), 3.31 (d, 1H, J = 11.2 Hz, OH), 2.35 (s, 3H), 2.24 (ddd, 1H, J = 14.2, 8.2, 7.3 Hz), 2.18 (d, 3H, J = 1.4 Hz), 1.65 (ddd, 1H, J = 14.2, 2.1, 2.0 Hz). ¹³C NMR (62.9 MHz, CDCl₃): δ = 213.5, 166.0, 159.1, 129.0, 80.7, 56.1, 51.8, 35.8, 31.0, 14.3. HRMS-ESI: m/z [M + Na]⁺ calcd for C₁₀H₁₄O₄ + Na: 221.0789, found 221.0784.

Procedure B (Wacker oxidation of 22): To a solution of PdCl₂ (3 mg, 0.017 mmol, 0.1 equiv.) at rt in DMF/H₂O (0.3 mL/0.1 mL) was added CuCl (16 mg, 0.165 mmol, 1 equiv.). The reaction was stirred at the same temperature for 1 h under an atmosphere of O₂ (balloon). Olefin 22 (30 mg, 0.165 mmol, 1 equiv.) was added and the reaction mixture was stirred at rt overnight then was quenched with a saturated solution of NH₄Cl and extracted with Et₂O (x3). The combined organic layers were washed with brine (x5), dried with MgSO₄ and filtered. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (Hept/EtOAc, 1:0 up to 1:1) to yield pure 18 as a yellow oil obtained (13 mg, 40%).

(±)-cís-Methyl 3-((tert-butyldimethylsilyl)oxy)-5-(methoxy(methyl)carbamoyl)-2-methylcyclopent-1-ene carboxylate (19)

To a solution of Weinreb amide 16 (300 mg, 1.23 mmol, 1 equiv.) in dry CH₂Cl₂ (10 mL) were added pyridine (0.3 mL, 3.69 mmol, 3 equiv.), TBSCl (369 mg, 2.46 mmol, 2 equiv.) and DMAP (15 mg, 0.123 mmol, 0.1 equiv.). The reaction mixture was stirred at rt for 5 days, then quenched with saturated aqueous solution of NaHCO₃ and extracted with CH₂Cl₂ (x3). The combined organic layers were washed with saturated aqueous CuSO₄, then brine and dried over MgSO₄ and filtered. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (Hept/EtOAc, 3:1 up to 1:1) to give 19 as colorless oil (341 mg, 78%). Rₐ 0.35 (Hept/EtOAc 1:1). ¹H NMR (360 MHz, CDCl₃): δ = 4.57 (br dd, 1H, J = 7.7, 7.3 Hz), 3.94 (m, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 3.14 (s, 3H), 2.48 (br ddd, 1H, J = 12.2, 7.7, 7.2 Hz), 2.01 (br s, 3H), 1.63 (br dt, 1H, J = 12.2, 8.6 Hz), 0.82 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H). ¹³C NMR (90.6 MHz, CDCl₃): δ = 174.9, 165.8, 157.5, 126.4, 79.3, 61.2, 51.2, 43.6, 37.6, 32.3, 25.6 (3 C), 17.9, 13.4, -4.5, -5.0. HRMS-ESI: m/z [M + Na]⁺ calcd for C₁₇H₃₁NO₅Si + Na: 380.1868, found 380.1881.

(±)-cís-Methyl 5-formyl-3-hydroxy-2-methylcyclopent-1-ene carboxylate (20)
To a solution of Weinreb amide 16 (300 mg, 1.23 mmol, 1 equiv.) in THF (10 mL) at 0 °C was added Cp₂ZrHCl (695 mg, 2.70 mmol, 2.1 equiv.). The reaction mixture was stirred at the same temperature for 2 h then added with SiO₂, filtered and washed with EtOAc (x3). The solvents were removed under reduced pressure. The crude product was purified by short path filtration on neutral silica (Hept/EtOAc, 1:0 up to 1:1) to give the labile aldehyde 20 as a yellow oil (88 mg, 39%). This labile aldehyde was used immediately for the subsequent reaction. Rₜ 0.40 (Hept/EtOAc 1:4). ¹H NMR (250 MHz, CDCl₃, major product): δ = 9.90 (d, 1H, J = 2.2 Hz), 4.55 (m, 1H), 3.86 (m, 1H), 3.76 (s, 3H), 3.17 (br d, 1H, J = 7.4 Hz), 2.66 (br d, 1H, J = 7.0 Hz, OH), 2.32 (br ddd, 1H, J = 14.2, 7.9, 7.5 Hz), 2.19 (br d, 3H, J = 1.3 Hz), 1.86 (br dt app, 1H, J = 14.2, 3.3 Hz). HRMS-ESI: m/z [M + Na]⁺ calc'd for C₇H₁₂O₄ + Na: 207.0633, found 207.0632.

(±)-cís-Methyl 3-((tert-butylidimethylsilyl)oxy)-5-formyl-2-methylcyclopent-1-enecarboxylate (21)

To a solution of the TBS-protected Weinreb amide 19 (500 mg, 1.40 mmol, 1 equiv.) in dry THF (10 mL) at 0 °C were added Cp₂ZrHCl (793 mg, 2.94 mmol, 2.1 equiv.). The reaction mixture was allowed to warm-up to rt for 1 h, then quenched with SiO₂ and filtered. The solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on neutral silica (Hept/EtOAc, 3:1 up to 1:1) to furnish pure aldehyde 21 as colorless oil (180 mg, 43%). Rₜ 0.75 (Hept/EtOAc 1:1). ¹H NMR (360 MHz, CDCl₃): δ = 9.57 (d, 1H, J = 3.6 Hz), 4.64 (br ddd, 1H, J = 6.8, 5.9 Hz), 3.75 (s, 3H), 3.51 (m, 1H), 2.37 (ddd, 1H, J = 13.2, 7.7, 7.3 Hz), 2.15 (d, 3H, J = 1.4 Hz), 1.75 (ddd, 1H, J = 13.2, 6.4, 5.9 Hz), 0.89 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H). ¹³C NMR (75.4 MHz, CDCl₃): δ = 200.6, 165.6, 160.9, 125.21, 79.7, 55.2, 51.6, 33.9, 25.8 (3 C), 18.1, 13.9, -4.4, -4.8. HRMS-ESI: m/z [M + Na]⁺ calc'd for C₁₅H₂₀O₄Si + Na: 321.1497, found 321.1492.

(±)-cís-Methyl 3-hydroxy-2-methyl-5-vinylcyclopent-1-enecarboxylate (22)

A solution of Ph₃PCH₂Br (171 mg, 0.48 mmol, 4 equiv.) in THF (1 mL) was cooled to 0 °C and added with a 0.7 M solution of KHMDS in toluene (0.7 mL, 0.48 mmol, 4 equiv.). The reaction was stirred at the same temperature for 30 min until total dissolution of solid. A solution of hydroxylaldehyde 20 (22 mg, 0.12 mmol, 1 equiv.) in THF (1 mL) was added dropwise. The reaction mixture was stirred for 2 h then quenched with saturated aqueous NaHCO₃ and extracted with Et₂O (x3). The combined organic layers were washed with brine, dried over MgSO₄ and filtered. The solvents were removed under reduced pressure and the crude product purified by flash column chromatography (Hept/EtOAc, 1:0 up to 1:1) to give hydroxydiene 22 as a
colorless oil (9 mg, 40%). R<sub>t</sub> 0.40 (Hept/EtOAc 1:1).<sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>): δ = 5.89 (ddd, 1H, J = 17.3, 10.0, 7.3 Hz), 5.07 (br dt, 1H, J = 17.3, 1.4 Hz), 5.00 (br d, 1H, J = 10.0 Hz), 4.53 (m, 1H), 3.73 (s, 3H), 3.47 (m, 1H), 2.51 (dt, 1H, J = 13.9, 7.7 Hz), 2.13 (br s, 3H), 1.59 dt, 1H, J = 13.6, 5.0 Hz).<sup>13</sup>C NMR (90.6 MHz, CDCl<sub>3</sub>): δ = 166.6, 154.4, 141.9, 132.2, 114.5, 80.4, 51.5, 47.2, 39.2, 14.0. HRMS-ESI: m/z [M + Na]<sup>+</sup> caleld for C<sub>10</sub>H<sub>14</sub>O<sub>3</sub> + Na: 205.0840, found 205.0837.

(±)-cis and (±)-trans-Methyl 3-((tert-butylmethyisilyl)oxy)-2-methyl-5-vinylcyclopent-1-ene-carboxylate (23)

A solution of Ph<sub>3</sub>PCH<sub>2</sub>Br (303 mg, 0.85 mmol, 2.1 equiv.) in THF (1 mL) was cooled to 0 °C and added with a 0.7 M solution of KHMDS in toluene (1.2 mL, 0.85 mmol, 2.1 equiv.). The reaction was stirred at the same temperature for 30 min as before. A solution of aldehyde 21 (120 mg, 0.85 mmol, 1 equiv.) in THF (1 mL) was added dropwise. The reaction mixture was stirred for 1h then quenched with saturated aqueous NaHCO<sub>3</sub> and extracted with Et<sub>2</sub>O (x3). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub> and filtered. The solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (Hept/EtOAc, 1:0 up to 1:1) to give the diene 23 as an unseparated 58:42 mixture of cis and trans-diastereomers (61 mg, 54%). R<sub>t</sub> 0.40 (Hept/EtOAc 1:1).<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>). Major cis-isomer, δ = 5.79 (m, 1H), 4.99 (m, 2H), 4.53 (dd, 1H, J = 7.2, 6.1 Hz), 3.71 (s, 3H), 3.38 (br ddd, 1H, J = 7.4 Hz), 2.40 (br dt, 1H, J = 13.2, 7.5 Hz), 2.05 (d, 3H, J = 1.2 Hz), 1.50 (br ddd, 1H, J = 12.4, 6.4, 6.0, Hz), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H). Minor trans-isomer. δ = 5.74 (m, 1H), 4.99 (m, 2H), 4.76 (t, 1H, J = 7.2 Hz), 3.71 (s, 3H), 3.62 (br t, 1H, J = 8.5 Hz), 2.12 (br ddd, 1H, J = 12.9, 7.2, 1.5 Hz), 2.09 (br s, 3H), 1.92 (br ddd, 1H, J = 12.8, 8.7, 7.5 Hz), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H).<sup>13</sup>C NMR (90.6 MHz, CDCl<sub>3</sub>). Major isomer, δ = 166.8, 155.3, 141.6, 133.5, 114.5, 79.9, 51.3, 47.3, 40.0, 26.1 (3 C), 18.4, 14.0, −4.1, −4.5. Minor isomer. δ = 160.8, 157.0, 140.73, 130.5, 113.9, 80.0, 51.4, 47.0, 40.8, 26.1 (3 C), 18.4, 13.7, −4.1, −4.5. HRMS-ESI: m/z [M + Na]<sup>+</sup> caleld for C<sub>16</sub>H<sub>23</sub>O<sub>3</sub> + Na: 319.1705, found 319.170.

(peaks corresponding to the expected aldehyde are reported)