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# How an Early or Late Transition State Impacts the Stereoselectivity of Tetrahydropyran Formation by Intramolecular oxa-Michael Addition

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## Supporting Information I: Experimental procedures

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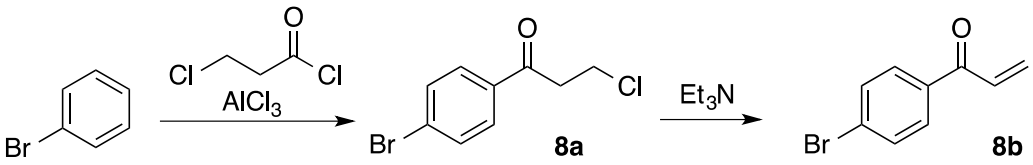
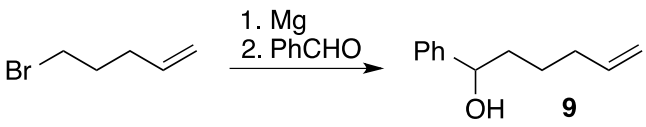
**General information**

Reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware. Anhydrous $CH_2Cl_2$ was freshly distilled from $CaH_2$ under nitrogen, anhydrous THF was freshly distilled from sodium metal and benzophenone under nitrogen, anhydrous toluene was freshly distilled from sodium metal under nitrogen. Anhydrous methanol was distilled from activated magnesium under nitrogen. Column chromatography was conducted using silica gel (230-400 mesh). All chemicals were obtained from commercial sources and used as received without purification unless indicated otherwise. [18]-Crown-6 were recrystalized according to the literature procedure.[1] $^1$H NMR spectra were recorded at 500 or 400 MHz in $CDCl_3$ solutions and $^{13}$C{H} NMR were recorded at the corresponding frequency. Chemical shifts are given in ppm, referenced to the residual chloroform (7.26 ppm, $^{13}$C-spectrum: 77.16 ppm). Coupling constants are in Hz. FTIR spectra were recorded using KBr plates. Only the most intense and/or diagnostic IR peaks are reported. High-resolution mass spectrometry (HRMS) measurements were performed using ESI-TOF employing the electrospray ionization technique (ESI) in methanol solutions.

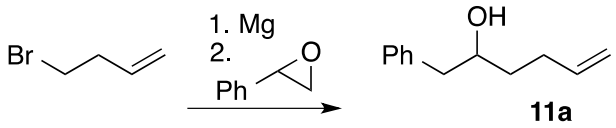



**1-(*p*-bromophenyl)-3-chloropropan-1-one (8a).**[2] 3-Chloropropanoyl chloride (2.54 g, 20 mmol, 1 eq.) in anhydrous $CH_2Cl_2$ (5 mL) was added dropwise to a mixture of bromobenzene (3.14 g, 20 mmol, 1 eq.) and $AlCl_3$ (6.13 g, 46 mmol, 2.3 eq.) in anhydrous $CH_2Cl_2$ (15 mL) at 40 °C. After stirring for 2 hours, the reaction was quenched with HCl (2M aq., 5 mL) and extracted with ether (3 × 20 mL). The organic extract was washed with water, sodium carbonate solution, again with water and subsequently dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent EtOAc/ hexane 5:95) to give ketone **8a** (359 mg, 60 %) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.82 (dt, *J* = 10.5, 2.1 Hz, 2H), 7.63 (dt, *J* = 10.5, 2.1 Hz, 2H), 3.91 (t, *J* = 6.9 Hz, 2H), 3.42 (t, *J* = 6.6 Hz, 2H).

**1-(*p*-bromophenyl)prop-2-en-1-one (8b)**.[3] Triethylamine (1.22 g, 12.1 mmol, 2 eq.) was added to a solution of 1-(*p*-bromophenyl)-3-chloropropan-1-one (1.50 g, 6.05 mmol,1 eq.) in $CH_2Cl_2$ (10 mL) and the mixture was stirred for 16 hours. The reaction was quenched by $NH_4Cl$ solution (15 mL) and separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were washed with $NH_4Cl$ solution, brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent EtOAc/Hexane 3:97) to give ketone **8b** (504 mg, 83%) as a yellow crystalline solid. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.81 (dt, *J* = 8.7, 2.4 Hz, 2H), 7.63 (dt, *J* = 8.7, 2.1 Hz, 2H), 7.11 (dd, *J* = 17.1, 10.8 Hz, 1H), 6.44 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.96 (dd, *J* = 10.5, 1.5 Hz, 1H); $^{13}$C{H} NMR (75 MHz, $CDCl_3$) $\delta$ 189.9, 136.0, 131.9, 130.7, 130.2, 128.2, 125.9.

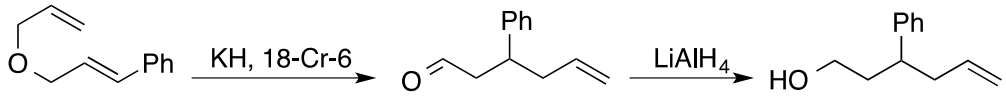


**1-phenylhex-5-en-1-ol (9)**.[4] A crystal of iodine was added to a suspension of magnesium (205 mg, 8.44 mmol, 2 eq.) in anhydrous ether (4 mL). The mixture was heated at reflux until the colour disappeared. A solution of 1-bromopentene (629 mg, 4.22 mmol, 1 eq.) in anhydrous ether (1 mL) was added dropwise and a gentle reflux was maintained. On completion, benzaldehyde (493 mg, 4.64 mmol, 1.1 eq.) was added to the mixture which was stirred at room temperature for 1 hour. The reaction mixture was diluted with water (10 mL) and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent EtOAc/ hexane 5:95) to afford 1-phenylhex-5-en-1-ol **9** (672 mg, 83 %) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.31-7.25 (m, 5H), 5.80 (ddt, *J* = 13.8, 9.9, 3.3 Hz, 1H), 4.95 (m, 2H), 4.68 (dt, *J* = 7.32, 1.84 Hz, 1H), 2.11-2.04 (m, 2H), 1.83-1.70 (m, 3H), 1.57-1.51 (m, 1H), 1.41-1.39 (m, 1H); $^{13}$C{H} NMR (75 MHz, $CDCl_3$) δ 144.8, 138.6, 128.5, 127.5, 125.9, 114.7, 74.5, 38.5, 33.6, 25.1.



**11a**

**2-phenylhex-5-en-1-ol (11a)**.[5] A crystal of iodine was added into a mixture of magnesium (711 mg, 29.6 mmol, 2 eq.) and anhydrous ether (10 mL). The mixture was heated at reflux until the reaction discoloured. A solution of 1-bromobutene (2 g, 14.8 mmol, 1 eq.) in anhydrous ether (4 mL) was added dropwise and a gentle reflux was maintained. The resulting Grignard solution was then added dropwise to a solution of styrene oxide (1.96 g, 16.3 mmol, 1.1 eq.) in anhydrous diethyl ether (3 mL). The mixture was stirred at room temperature for 1 h, then quenched with saturated aqueous $NH_4Cl$ solution (15 mL). The mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent EtOAc/Hexane 8:92) to afford 2-phenylhex-5-en-1-ol **11a** (1.67 g, 32%) as a colourless oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.36-7.19 (m, 5H), 5.75 (ddt, *J* = 13.8, 9.9, 3.3 Hz, 1H), 4.99-4.92 (m, 2H), 3.79-3.68 (m, 2H), 2.83-2.76 (m, 1H), 2.00-1.92 (m, 2H), 1.81-1.66 (m, 2H), 1.35 (s, 1H); $^{13}$C{H} NMR (75 MHz, $CDCl_3$) δ 138.4, 128.7, 128.3, 128.1, 126.8, 114.8, 60.4, 48.0, 31.4, 31.2.

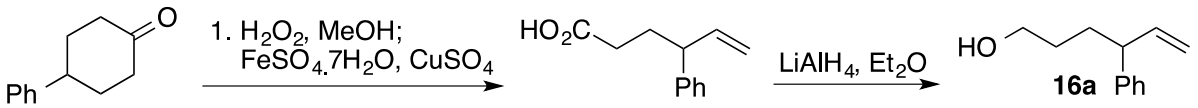


**13** **14c** **14a**

**3-phenylhex-5-enal (14c).**[6] 18-crown-6 (228 mg, 0.861 mmol, 1.5 eq.) in dry THF (5 ml) was added to a suspension of potassium hydride in oil suspension (96 mg, 1.43 mmol, 60%, 2.5 eq.) in anhydrous THF (25 ml). The mixture was stirred for 15 minutes. A solution of allyl cinnamyl ether (**13**) (100 mg, 0.574 mmol, 1 eq.) in THF (3 mL) was added in one portion. The mixture was stirred for 1.5 h before the dark brown solution was poured onto a mixture of ice and phosphate buffer (pH 7.0) (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent EtOAc/Hexane 10:90) to give aldehyde **14c** as a yellow oil (75 mg, 75%). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.17-7.31 (m, 5H), 5.65 (ddt, J = 13.5, 7, 3.5 Hz,

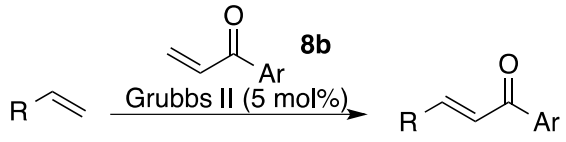
1H), 4.92-5.00 (m, 2H), 3.44-3.57 (m, 2H), 2.77-2.83 (m, 1H), 2.38 (t, J = 7 Hz, 2H), 1.96-2.03 (m, 1H), 1.21 (brs, 1H)

**3-phenylhex-5-en-1-ol (14a).**[7] A solution of 3-phenylhex-5-enal **14c** (75.4 mg, 0.433 mmol, 1 eq.) in diethyl ether (4 mL) was added dropwise to a suspension of $LiAlH_4$ (32.8 mg, 0.866 mmol, 2 eq.) in anhydrous diethyl ether (5 mL) at 0 °C. The mixture was warmed to room temperature and stirred overnight. The mixture was carefully quenched with water (5 mL), and the resulting white suspension was filtered through Celite, washing with $CH_2Cl_2$ and concentrated under reduced pressure to give 4-phenylhex-5-en-1-ol **14a** as a brown oil. The residue was purified by column chromatography (eluent EtOAc/Hexane 15:85) to afford 3-phenylhex-5-en-1-ol (**14a**, 74 mg, 97%) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.17-7.31 (m, 5H), 5.65 (ddt, *J* = 13.5, 7, 3.5 Hz, 1H), 4.92-5.00 (m, 2H), 3.44-3.57 (m, 2H), 2.77-2.83 (m, 1H), 2.38 (t, *J* = 7 Hz, 2H), 1.96-2.03 (m, 1H), 1.21 (brs, 1H); $^{13}$C{H} NMR (125 MHz, $CDCl_3$) $\delta$ 144.5, 136.7, 128.5, 127.6, 126.3, 116.2, 61.1, 42.3, 41.4, 38.6.




**4-phenylhex-5-enoic acid.**[8] Aqueous $H_2O_2$ (0.45 mL, 5.74 mmol, 2 eq.) was added dropwise to a stirred solution of 4-phenylcyclohexanone (500 mg, 2.87 mmol, 1 eq.) at 25 °C. The mixture was stirred for 3 h, then added dropwise to a solution of of $FeSO_4.6H_2O$ (1.60 g, 5.74 mmol, 2 eq.) and $CuSO_4.5H_2O$ (1.43 g, 2.74 mmol, 1 eq.) in water (40 mL). The mixture was stirred overnight at room temperature, then extracted with ether (3 × 20 mL). The combined organic extracts were extracted with aqueous sodium hydroxide (20%, 2 x 10 mL). The combined alkaline extracts were brought to pH 2 with aqueous sulfuric acid (20%, 25 mL) and extracted with ether (3 × 20 mL). The combined organic extracts were washed with water, brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the acid which was used in the next step without further purification. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34-7.18 (m, 8H), 5.94 (ddt, *J* =13.8, 9.9, 3.3 Hz, 1H), 5.10 (m, 1H), 5.06-5.05 (m, 1H), 2.36-2.31 (m, 2H), 2.30-2.00 (m, 3H), 1.83-1.70 (m, 3H), 1.57-1.51 (m, 1H), 1.41-1.39 (m, 1H).

**4-phenylhex-5-en-1-ol (16a)**.[9] $LiAlH_4$ (218 mg, 5.74 mmol, 2 eq.) was suspended in diethyl ether. A solution of 4-phenylhex-5-enoic acid (546 mg, 2.87 mmol, 1 eq.) in diethyl ether was subsequently added dropwise to the mixture at 0 °C. The reaction mixture was then warmed to room temperature and stirred overnight. The reaction mixture was carefully quenched with water (5 mL), and the resulting white suspension was filtered through Celite, washing with $CH_2Cl_2$ (3 × 10 mL) and concentrated under reduced pressure to give a brown oil. The oil was purified by column chromatography (eluent EtOAc/Hexane 20:80) to afford 4-phenylhex-5-en-1-ol **16a** (134 mg, 32%) as a colourless oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.32-7.17 (m, 5H), 5.96 (ddt, *J* = 13.8, 9.9, 3.3 Hz, 1H), 5.06 (dt, *J* = 6.0, 1.2 Hz, 1H), 5.01 (d, *J* = 1.2 Hz, 1H), 3.63 (t, *J* = 6.6 Hz, 2H), 3.26 (q, *J* = 7.5 Hz, 1H), 1.82-1.76 (m, 2H), 1.61-1.47 (m, 3H); $^{13}$C{H} NMR (75 MHz, $CDCl_3$) $\delta$ 144.2, 142.1, 128.5, 127.6, 126.3, 114.2, 62.9, 49.7, 31.5, 30.8.

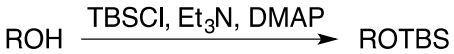


**General method for cross-metathesis reaction with 1-(*p*-bromophenyl)prop-2-en-1-one.** The phenylalkenol (0.567 mmol, 100 mg, 1 eq.) and 1-(*p*-bromophenyl)prop-2-en-1-one (**8b**) (1.70 mmol, 359 mg, 3 eq.) was dissolved in distilled $CH_2Cl_2$ under nitrogen. The solution was heated at reflux while a solution of the Grubbs II catalyst (0.028 mmol, 24 mg, 0.05 eq.) in distilled $CH_2Cl_2$ (5 mL) and was added at 0.5 h intervals in portions of 1 mL. The mixture was heated at reflux for 2 h, then cooled to room temperature and filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (eluent EtOAc/hexane 20:80) to afford the oxa-Michael precursors as oils.

**(*E*)-1-(*p*-bromophenyl)-7-hydroxy-7-phenylhept-2-en-1-one** (**10b**). Colourless oil (76%); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.77 (dd, *J* = 6.6, 2.1 Hz, 2H), 7.59 (dd, *J* = 6.6, 2.1 Hz, 2H), 7.58-7.07 (m, 8H), 7.07-6.99 (m, 1H), 6.80 (dt, *J* = 15.6, 1.2 Hz, 1H), 4.73-4.69 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 1H), 2.36-2.26 (m, 3H), 1.87-1.53 (m, 9H).

**(*E*)-1-(*p*-bromophenyl)-7-hydroxy-6-phenylhept-2-en-1-one** (**12b**). Colourless oil (18%); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.85 (dd, *J* = 8.7, 2.1 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.37-7.20 (m, 12H), 7.18-6.98 (m, 1H), 6.74 (d, *J* = 15.3 Hz, 2H), 4.04-3.97 (m, 1H), 3.76 (d, *J* = 6.6 Hz, 2H), 3.46 (t, *J* = 11.4 Hz, 1H), 3.30 (dd, *J* = 16.2, 6.9 Hz, 1H), 2.86-2.78 (m, 3H), 2.26-2.19 (m, 3H), 2.04-1.25 (m, 12H).

**(*E*)-1-(*p*-bromophenyl)-7-hydroxy-4-phenylhept-2-en-1-one** (**17b**). Colourless oil (**%); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.77 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.60 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.36-7.17 (m, 16H), 6.82 (dd, *J* = 15.3, 1.2 Hz, 1H), 3.70-3.65 (m, 2H), 3.56 (q, *J* = 7.7 Hz, 1H), 2.06 (s, 1H), 1.99-1.94 (m, 2H), 1.56 (m, 13H), 1.31-1.26 (m, 2H).




**General method for TBS protection.** TBSCl (513 mg, 3.40 mmol, 3 eq.) in $CH_2Cl_2$ (0.5 mL) was added dropwise to a solution of the alcohol (200 mg, 1.14 mmol, 1 eq.), triethylamine (633 µL, 4.54 mmol, 4 eq.) and DMAP (2.77 mg, 0.023 mmol, 0.02 eq.) in $CH_2Cl_2$ (1 mL) at 0 °C. The solution was then stirred overnight. The reaction was quenched with water. The organic layer was separated, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (eluent EtOAc/hexane 5:95) to afford the TBS ethers.

***t*-butyldimethyl((2-phenylhex-5-en-1-yl)oxy)silane (11b).** Colourless oil (64%); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.25-7.29 (m, 5H), 5.82-5.90 (m, 1H), 4.99-5.04 (m, 2H), 3.74-3.79 (m, 2H), 2.80-2.85 (m, 1H), 2.00-2.06 (m, 3H), 1.73-1.75 (m, 1H), 0.94 (s, 14H), 0.02-0.12 (m, 9H); $^{13}$C{H} NMR (125 MHz, $CDCl_3$) $\delta$ 143.1, 138.8, 129.1, 128.2, 128.2, 126.3, 125.3, 114.4, 68.1, 48.0, 31.6, 31.0, 25.9, 25.7, 25.7, 18.3, 18.2, -2.91, -2.99, -5.5; FTIR (neat) cm$^{-1}$: 1605, 1641, 1495, 1256, 1213, 966, 910; MS (ESI): $[M + H]^+$ m/z 291; HRMS (ESI-TOF): $[M + H]^+$ calcd. for $C_{18}H_{30}OSi$: 291.2144; found: 291.2139.

***t*-butyldimethyl((3-phenylhex-5-en-1-yl)oxy)silane (14b).** Colourless oil (96%); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.17-7.32 (m, 5H), 5.65-5.70 (m, 1H), 4.94-5.01 (m, 2H), 3.41-3.55 (m, 2H), 2.84-2.86 (m, 1H), 1.93-2.00 (m, 1H), 1.81 (s, 1H), 0.91 (s, 10H), 0.01 (s, 6H); $^{13}$C{H} NMR (100 MHz, $CDCl_3$) $\delta$ 144.8, 137.0, 128.2, 127.8, 126.1, 115.9, 61.0, 42.0, 21.2, 38.8, 26.0, 25.7, 18.3, -2.93; FTIR (neat) cm$^{-1}$: 1639, 1603, 1493, 1257, 1217, 995, 912; MS (ESI): $[M + H]^+$ m/z 291; HRMS: $[M + H]^+$ calcd. for $C_{18}H_{30}OSi$: 291.2144; found: 291.2117.

***t*-butyldimethyl((4-phenylhex-5-en-1-yl)oxy)silane (16b).** Colourless oil (84%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.15-7.28 (m, 5H), 5.88-5.95 (m, 1H), 4.92-5.02 (m, 2H), 3.55-3.58 (m, 2H), 3.22 (app. q, *J* = 7 Hz, 1H), 1.70-1.77 (m, 2H), 1.38-1.53 (m, 3H), 1.23 (s, 10H), 0.01 (s, 7H); $^{13}$C{H} NMR (100 MHz, $CDCl_3$) $\delta$ 144.4, 142.4, 128.5, 128.3, 127.6, 126.8, 126.2, 114.0, 63.1, 49.6, 31.6, 30.8, 26.0, 18.4, -5.3; FTIR (neat) cm$^{-1}$: 1635, 1601, 1493, 1254, 1186, 972, 912; MS (ESI): $[M + H]^+$ m/z 291; HRMS: $[M + H]^+$ calcd. for $C_{18}H_{30}OSi$: 291.2144; found: 291.2158.


**General method for Ozonolysis-Wittig reaction.** Ozone in oxygen was bubbled through a solution of the alkene (169 mg, 0.58 mmol, 1 eq.) in $CH_2Cl_2$ (10 mL) for 15 minutes at -78 °C. On completion, dimethyl sulphide (86 μL, 1.166 mmol, 2 eq.) was added. The solution was stirred at room temperature for 1 hour. The mixture was concentrated under reduced pressure to yield the aldehyde which was used in the next step without purification.

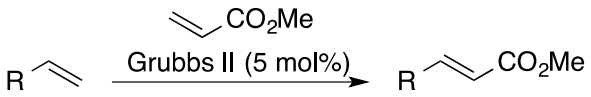
**General method for Wittig reaction.** 1-(*p*-Bromophenyl)-2-(triphenyl-λ$^5$-phosphaneylidene)ethan-1-one[10] (269 mg, 0.59 mmol, 1.2 eq.) was added to a solution of the aldehyde (143 mg, 0.487 mmol, 1 eq.) in anhydrous $CH_2Cl_2$ (5 mL). The mixture was heated at reflux overnight. The mixture was concentrated to a quarter of its original volume and filtered through Celite, washing with hexane. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (eluent EtOAc/ hexane 5:95) to give the oxa-Michael precursors as oils.

**(*E*)-1-(*p*-bromophenyl)-7-((*tert*-butyldimethylsilyl)oxy)-6-phenylhept-2-en-1-one** (**12c**). Colourless oil (57%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.74-7.76 (m, 2H), 7.58-7.61 (m, 2H), 7.16-7.33 (m, 8H), 7.01-7.05 (m, 1H), 6.74 (d, J = 16 Hz, 1H), 3.65-3.75 (m, 2H), 2.73-2.82 (m, 2H), 2.19-2.25 (m, 2H), 2.09-2.15 (m, 1H), 1.75-1.85 (m, 1H), 1.60-1.67 (m, 2H), 0.84-0.88 (m, 15H), -(0.43-0.01) (m, 8H); $^{13}$C{H} NMR (100 MHz, $CDCl_3$) $\delta$ 189.7, 150.4, 142.2, 136.7, 131.8, 130.1, 129.6, 128.4, 128.1, 127.7, 126,6, 125.5, 68.0, 48.2, 30.8, 30.2, 25.9, 18.2, -4.7; FTIR (neat) cm$^{-1}$: 1670, 1585, 1566, 1543, 1396, 1360, 1253, 1220, 606; MS (ESI): m/z 474; HRMS (ESI-TOF): $[M + H]^+$ calcd. for $C_{25}H_{33}BrO_2Si$: 473.1511; found: 473.1524.

**(*E*)-1-(*p*-bromophenyl)-7-((*tert*-butyldimethylsilyl)oxy)-5-phenylhept-2-en-1-one** (**15c**). Colourless oil (37%); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.60-7.69 (m, 4H), 7.24-7.41 (m, 5H), 6.75-6.99 (m, 1H), 6.72 (m, 1H), 3.46-3.66 (m, 2H), 3.04-3.10, (m, 1H), 2.60-2.80 (m, 2H), 1.85-2.12 (2H), 0.97 (m, 10H), 0.08 (m, 6H); $^{13}$C{H} NMR (100 MHz, $CDCl_3$) $\delta$ 202.0, 143.4, 128.6, 128.6, 127.7, 127.6, 126.7, 126.6, 102.6, 93.9, 60.6, 60.4, 39.7, 39.3, 38.6, 38.0, 25.9, 18.3, 1.03, -4.7; FTIR (neat) cm$^{-1}$: 1670, 1585, 1566, 1543, 1396, 1360, 1258, 1223, 663; MS (ESI): m/z 474; HRMS: $[M + H]^+$ calcd. for $C_{25}H_{33}BrO_2Si$: 473.1511; found: 473.1508.

**(*E*)-1-(*p*-bromophenyl)-7-((*tert*-butyldimethylsilyl)oxy)-4-phenylhept-2-en-1-one** (**17c**). Colourless oil (35%); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.74 (dd, J = 9, 1.5 Hz, 2H), 7.59 (dd, *J* = 7, 2 Hz, 2H), 7.15-7.26 (m, 10H), 6.78 (dd, *J* = 15.5, 1 Hz, 1H), 3.71 (t, *J* = 6 Hz, 1H), 3.61 (t, *J* = 6.5 Hz, 2H), 3.52 (q, *J* = 7.5 Hz, 1H), 3.07 (t, *J* = 7.5 Hz, 1H) 1.86-1.99 (m, 11H), 0.86-0.89 (m, 19H), 0.00-0.05 (m, 12H); $^{13}$C{H} NMR (100 MHz, $CDCl_3$) $\delta$ 200.8, 136.4, 131.8, 130.1, 129.1, 128.8, 128.5, 127.8, 127.6, 126.6, 62.7, 58.9, 31.5, 30.7, 30.2, 26.1, 26.0, 18.3,

-4.7; FTIR (neat) $cm^{-1}$: 1670, 1585, 1566, 1543, 1396, 1360, 1256, 1220, 661; MS (ESI): m/z 474; HRMS (ESI-TOF): $[M + H]^+$ calcd. for $C_{25}H_{33}BrO_2Si$: 473.1511; found: 473.1524.




**General procedure for the cross-metathesis reaction with methyl acrylate.** To a solution of the phenylalkenol (1.1 mmol, 1 eq.) in distilled $CH_2Cl_2$ was added methyl acrylate (3.4 mmol, 3 eq.) under gentle nitrogen flow. After 15 mins, a solution of the Grubbs II catalyst (0.06 mmol, 0.05 eq. $c$ = 0.05 mol/$dm^3$) in dry $CH_2Cl_2$ was added dropwise at reflux. The reaction was monitored by TLC (Hexane/EtOAc 80:20) and upon completion (2-4 h) the reaction was left open to air overnight. Purification of the crude mixture by flash column chromatography (eluents: 95:5, 90:10, 80:10, 70:10 Hexane/EtOAc respectively) furnished the oxa-Michael precursors as oils.

**(*E*)-methyl 7-hydroxy-7-phenylhept-2-enoate** (**10a**). Colourless oil (93%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.26-7-38 (m, 5H), 6.92 (dt, $J$ = 15.6, 7.0 Hz, 1H), 5.79 (dt, $J$ = 15.6, 1.5 Hz, 1H), 4.66-4.70 (m, 1H), 3.12 (s, 3H), 2.21 (qd, $J$ = 7.0, 1.5 Hz, 2H), 1.56-1.86 (m, 3H), 1.40-1.52 (m, 1H) ppm; $^{13}$C{H} NMR (100 MHz, $CDCl_3$): $\delta$ 24.4, 32.2, 51.6, 74.5, 121.3, 126.0, 127.8, 128.7, 144.7, 149.2, 167.2 ppm; FTIR: 1647, 1431, 1273, 1200, 1147, 569 $cm^{-1}$; HRMS (ESI-TOF) m/z: Calculated for $C_{14}H_{19}O_3$ $(M+H)^+$: 235.1334, Found: 235.1333.

**(*E*)-methyl 7-hydroxy-6-phenylhept-2-enoate** (**12a**). Colourless oil (75%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.19-7.21 (m, 2H), 7.25-7.28 (m, 1H), 7.33-7.36 (m, 2H), 6.91 (dt, $J$ = 15.7, 6.9 Hz, 1H), 5.76 (dt, $J$ = 15.7, 1.6 Hz, 1H), 3.74 (br d, $J$ = 6.8 Hz, 2H), 2.8 (dtd, $J$ = 11.5, 6.6, 5.0 Hz, 1H), 2.07-2.13 (m, 2H), 1.89 (dddd, $J$ = 13.6, 8.8, 7.0, 5.0 Hz, 1H), 1.75 (dddd, $J$ = 13.6, 10.1, 8.1, 6.6 Hz, 1H) ppm; $^{13}$C{H} NMR (100 MHz, $CDCl_3$): $\delta$ 30.0, 30.3, 48.1, 51.6, 67.5, 121.4, 127.2, 128.2, 129.0, 141.5, 149.0, 167.2 ppm; FTIR: 1746, 1651, 1107, 1088, 698, 515 $cm^{-1}$; HRMS (ESI-TOF) m/z: Calculated for $C_{14}H_{19}O_3$ $(M+H)^+$: 235.1334 Found: 235.1337.

**(*E*)-methyl 7-hydroxy-5-phenylhept-2-enoate** (**15a**). Colourless oil (80%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.16-7.23 (m, 3H), 7.29-7.32 (m, 2H), 6.82 (dt, $J$ = 15.6, 7.3 Hz, 1H), 5.77 (dt, $J$ = 15.6, 1.5 Hz, 1H), 3.68 (s, 3H), 3.52-3.59 (m, 1H), 3.42-3.49 (m, 1H), 2.88-2.95 (m, 1H), 2.53 (td, $J$ = 7.3, 1.4 Hz, 2H), 1.97 (dddd, $J$ = 14.1, 7.7, 6.8, 4.8 Hz, 1H), 1.82 (dddd, $J$ = 14.1, 10.2, 6.1, 5.3 Hz, 1H), 1.20 (t, $J$ = 5.2 Hz) ppm; $^{13}$C{H} NMR (100 MHz, $CDCl_3$): $\delta$ 38.8, 39.8, 41.8, 60.9, 122.6, 126.8, 127.6, 128.8, 143.6, 147.3, 167.0 ppm; FTIR: 1697, 1651, 1495, 1435, 1277, 1211, 1159, 1041, 986, 764, 702, 553 $cm^{-1}$; HRMS (ESI-TOF) m/z: Calculated for $C_{14}H_{19}O_3$ $(M+H)^+$: 235.1334, Found: 235.1335.

**(*E*)-methyl 7-hydroxy-4-phenylhept-2-enoate** (**17a**). Colourless oil (86%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.30-7.33 (m, 2H), 7.21-7.26 (m, 1H), 7.17-7.19 (m, 2H), 7.07 (dd, $J$ = 15.6, 7.9 Hz, 1H), 5.80 (dt, $J$ = 15.7, 1.2 Hz, 1H), 3.71 (s, H), 3.61 (t, $J$ = 6.4 Hz, 2H), 3.41 (q, $J$ = 7.6 Hz, 1H), 1.79-1.94 (m, 2H), 1.44-1.62 (m, 2H) ppm; $^{13}$C{H} NMR (100 MHz, $CDCl_3$): $\delta$ 30.7, 31.2, 48.4, 51.7, 62.7, 120.6, 127.1, 127.9, 128.9, 142.0, 151.9, 167.2 ppm; FTIR: 1715, 1645, 1495, 1454, 1435, 1275, 1173, 1057, 737, 700, 517 $cm^{-1}$; HRMS (ESI-TOF) m/z: Calculated for $C_{14}H_{19}O_3$ $(M+H)^+$: 235.1334, Found: 235.1332.

**General procedure for acid-catalyzed oxa-Michael addition.** Amberlyst®-15 was added to a solution of the alcohol or TBS-protected alcohol (0.1 mmol, 1 eq.) in methanol. The mixture

was stirred for 15 hours. Upon completion, the mixture was filtered through Celite, washing with $CH_2Cl_2$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (Hexane/EtOAc 90:10) to give the tetrahydropyran.

**1-(*p*-bromophenyl)-2-((2*S*,6*R*)-6-phenyltetrahydro-2*H*-pyran-2-yl)ethan-1-one** (***cis*-18**). Yellow oil (84%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.83-7.86 (m, 2H), 7.56-7.60 (m, 2H), 7.19-7.31 (m, 5H), 4.41 (dd, *J* = 11.2, 2 Hz, 1H), 4.11-4.17 (m, 1H), 3.36 (dd, *J* = 16, 6.4 Hz,3.0 1H), 3.00 (dd, *J* = 15.6, 6 Hz, 1H), 1.93-1.98 (m, 1H), 1.69-1.88 (m, 3H), 1.34-1.55 (m, 2H); $^{13}$C{H} NMR (100 MHz, $CDCl_3$) $\delta$ 197.7, 143.1, 136.3, 131.8, 130.0, 128.2, 127.2, 125.7, 79.8, 75.0, 45.5, 33.3, 31.4, 23.9; FTIR (Neat) cm$^{-1}$: 2932, 2854, 1682, 1582, 702; MS (ESI): m/z 359; HRMS: $[M + H]^+$ calcd. for $C_{19}H_{19}BrO_2$: 359.0647; found: 359.0641.

**1-(*p*-bromophenyl)-2-((2S,5S)-5-phenyltetrahydro-2H-pyran-2-yl)ethanone** (***trans*-19**). Yellow crystals (77%); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.85 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.19-7.32 (m, 6H), 4.12 (app q, *J* = 7 Hz, 2H), 3.97-4.05 (m, 2H), 3.44-3.51 (m, 1H), 3.32 (dd, *J* = 16, 7 Hz, 1H), 2.95 (dd, J = 10.5, 5.5 Hz, 1H), 2.79-2.86 (m, 1H), 1.80-1.94 (m, 3H), 1.51-1.59 (m, 2H); $^{13}$C{H} NMR (125 MHz, $CDCl_3$) $\delta$ 197.3, 142.1, 136.0, 132.0, 129.9, 128.6, 127.4, 126.7, 74.1, 73.9, 45.0, 42.6, 31.9, 24.7; FTIR (neat) cm$^{-1}$: 1643, 586; MS (ESI): $[M + H]^+$ m/z 360; HRMS: $[M + H]^+$ calcd. for $C_{19}H_{19}BrO_2$: 359.0647; found: 359.0646; M.P.: 104-107 °C.

**1-(*p*-bromophenyl)-2-((2*S*,5*S*)-4-phenyltetrahydro-2*H*-pyran-2-yl)ethan-1-one** (***cis*-20**). Yellow crystals (68%); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.83 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.19-7.32 (m, 5H), 4.04-4.14 (m, 2H), 3.58-3.63 (m, 1H), 3.32 (dd, *J* = 16, 7 Hz, 1H), 2.82-2.94 (m, 2H), 1.97 (d, *J* = 13 Hz, 1H), 1.75-1.82 (m, 2H), 1.54 (q, *J* = 11.5 Hz, 1H); $^{13}$C{H} NMR (100 MHz, $CDCl_3$) $\delta$ 197.2, 145.4, 136.0, 131.9, 129.8, 128.6, 128.4, 126.8, 126.4, 74.3, 68.3, 45.1, 41.6, 39.5, 33.2; FTIR (neat) cm$^{-1}$: 1676, 1603, 1502, 511; MS (ESI): $[M + H]^+$ m/z 359; HRMS: $[M + H]^+$ calcd. for $C_{19}H_{19}BrO_2$: 359.0647; found: 359.0641; M.P.: 80-85 °C.

**1-(*p*-bromophenyl)-2-((2R,3R)-3-phenyltetrahydro-2H-pyran-2-yl)ethanone** (***trans*-21**). Yellow crystals (quant.); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.65-7.67 (m, 2H), 7.51-7.54 (m, 2H), 7.21-7.32 (m, 5H), 4.14 (dt, J = 10, 2 Hz, 1H), 3.99 (dt, *J* = 11.5, 2 Hz, 1H), 3.55 (dt, *J* = 11.5, 2 Hz, 1H), 3.03 (dd, *J* = 15.5, 10 Hz, 1H), 2.63 (dd, *J* = 15.5, 2 Hz, 1H), 1.99-2.04 (m, 1H), 1.73-1.85 (m, 2H), 1.67-1.71 (m, 1H), 1.24-1.34 (m, 1H); $^{13}$C{H} NMR (125 MHz, $CDCl_3$) $\delta$ 197.9, 142.8, 136.1, 131.7, 129.8, 128.8, 128.0, 127.8, 127.0, 78.7, 68.5, 48.7, 42.9, 32.4, 29.7, 26.3; FTIR (neat) cm$^{-1}$: 1643, 586; MS (ESI): m/z 359; HRMS: $[M + H]^+$ calcd. for $C_{19}H_{19}BrO_2$: 359.0647; found: 359.0642; M.P.: 123-125 °C.

**General procedure for *t*-BuOK catalyzed oxa-Michael addition.** A solution of the alcohol (0.1 mmol) in anhydrous THF (1 ml) was added dropwise by syringe to a solution of *t*-BuOK in THF (0.2 eq.) at -78°C, placing the needle against the wall of the round-bottom flask. The mixture was stirred for 45 mins at -78 ºC then quenched by adding aqueous $NH_4Cl$ solution (1 ml). The mixture was allowed to warm to room temperature and diluted with diethyl ether (2 ml) while stirring. The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2 ml) twice. The combined organic phases were dried ($Na_2SO_4$), then filtered through a silica/Celite pad washing with diethyl ether, and finally concentrated *in vacuo* to yield a yellow oil.

**General procedure for *t*-BuOK catalyzed oxa-Michael addition in the presence of [18]-Crown-6.** A solution of *t*-BuOK in THF (0.2 eq.) was added to a solution of [18]-Crown-6 (0.1

mmol,1 eq.) in dry THF (0.5 ml) at room temperature. The mixture was stirred for 15 mins. Then cooled to -78 ºC and stirred for 10 mins. A solution of the alcohol (0.1 mmol, 1 eq.) in dry THF (0.5 ml) was added dropwise by syringe, placing the needle against the wall of the round-bottom flask. The reaction was stirred for 45 mins at -78 ºC then quenched by adding aqueous $NH_4Cl$ solution (1 ml). The mixture was allowed to warm to room temperature and diluted with diethyl ether (2 ml) while stirring. The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2 ml) twice. The combined organic phase was dried over $Na_2SO_4$, then filtered through a silica/Celite pad, washing with diethyl ether, and concentrated *in vacuo* to yield a yellow oil.

**General procedure for TBAF or DBU catalyzed oxa-Michael addition.** To a solution of alcohol (0.1 mmol, 1 eq.) in dry THF (1 ml) was added TBAF (1 eq.) or DBU (1 eq.) in one portion at room temperature. The mixture was stirred for 15 hours, then filtered through a silica/Celite pad, washing with diethyl ether, and concentrated *in vacuo* to yield a yellow oil.

***trans* methyl 2-(6-phenyltetrahydro-2H-pyran-2-yl)acetate** (***trans*-22**). Colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7-24-7.27 (m, 1H), 7.33-7.39 (m, 4H), 4.88 (t, *J* = 5.7 Hz, 1H), 4.20-4.26 (m, 1H), 3.70 (s, 3H), 2.75 (dd, *J* = 14.7, 8.6 Hz, 1H), 2.50 (dd, *J* = 14.7, 5.7 Hz, 1H), 1.87-2.03 (m, 2H), 1.66-1.78 (m, 3H), 1.45-1.53 (m, 1H) ppm; $^{13}$C{H} NMR (100 MHz, $CDCl_3$): $\delta$ 18.9, 29.5, 30.0, 39.4, 51.8, 68.8, 73.0, 126.7, 127.2, 128.5, 141.6, 172.0 ppm; FTIR: 1738, 1495, 1435, 1346, 1287, 1262, 1202, 1173, 1142, 1094, 1072, 1020, 793, 756, 727, 700 cm$^{-1}$; HRMS (ESI-TOF) m/z: Calculated for $C_{14}H_{19}O_3$ $(M+H)^+$: 235.1334, Found: 235.1339.

***cis* methyl 2-(6-phenyltetrahydro-2H-pyran-2-yl)acetate** (***cis*-22**). Colourless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.22-7.25 (m, 1H), 7.29-7.34 (m, 4H), 4.4 (dd, *J* = 11.3, 2.2 Hz, 1H), 3.95-4.01 (m, 1H), 3.68 (s, 3H), 2.66 (dd *J* = 15.1, 7.1 Hz, 1H), 2.48 (dd, *J* = 15.1, 6.0 Hz, 1H), 1.92-1.99 (m, 1H), 1.84-1.87 (m, 1H), 1.71-1.78 (m, 2H), 1.44-1.56 (m, 1H), 1.29-1.42 (m, 1H) ppm; $^{13}$C{H} NMR (100 MHz, $CDCl_3$): $\delta$ 23.8, 30.9, 33.2, 41.6, 51.6, 74.7, 79.6, 125.7, 127.2, 128.2, 143.1, 171.8 ppm; FTIR: 1740, 1645, 1491, 1437, 1198, 1086, 1044, 926, 754, 698, 522 cm$^{-1}$; HRMS (ESI-TOF) m/z: Calculated for $C_{14}H_{19}O_3$ $(M+H)^+$: 235.1334, Found: 235.1336.

***trans* methyl 2-(5-phenyltetrahydro-2H-pyran-2-yl)acetate** (***trans*-23**).[11] Yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.18-7.33 (m, 5H), 4.01 (ddd, *J* = 11.3, 4.4, 2.3 Hz, 1H), 3.81-3.88 (m, 1H), 3.46 (t, *J* = 11.3 Hz, 1H), 2.78-2.85 (m, 1H), 2.59 (dd, *J* = 15.2, 7.8 Hz, 1H), 2.47 (dd, *J* = 15.2, 5.2 Hz, 1H), 2.03-2.07 (m, 1H), 1.76-186 (m, 2H), 1.50-1.57 (m, 1H) ppm; $^{13}$C{H} NMR (100 MHz, $CDCl_3$): $\delta$ 30.6, 31.7, 41.5, 42.7, 52.0, 74.1, 74.4, 127.0, 127.6, 128.8, 142.3, 172.1 ppm; FTIR: 1738, 1636, 1493, 1437, 1196, 1163, 1109, 1086, 1007, 758, 700, 527 cm$^{-1}$; HRMS (ESI-TOF) m/z: Calculated for $C_{14}H_{19}O_3$ $(M+H)^+$: 235.1334, Found: 235.1338.

***trans* methyl 2-(4-phenyltetrahydro-2H-pyran-2-yl)acetate** (***trans*-24**). Colourless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.20-7.35 (m, 5H), 4.35 (dt, *J* = 10.2, 5.4 Hz, 1H), 3.73-3.85 (m, 2H), 3.71 (s, 3H), 3.02-3.11 (m, 1H), 2.83 (dd, *J* =14.9, 8.4 Hz, 1H), 2.53 (dd, *J* =14.9, 5.9 Hz, 1H), 2.10 (ddd, *J* = 13.5, 8.8, 4.3 Hz, 1H), 1.89-1.93 (m, 2H), 1.78 (dt, *J* = 13.5, 4.8 Hz, 1H) ppm; $^{13}$C{H} NMR (100 MHz, $CDCl_3$): $\delta$ 32.2, 35.3, 35.8, 38.3, 51.9, 62.5, 69.9, 126.4, 127.3, 128.7, 144.6, 171.9 ppm; FTIR: 1738, 1634, 1440, 1385,1260, 1204, 1153, 1086, 1034, 766, 700, 500 cm$^{-1}$; HRMS (ESI-TOF) m/z: Calculated for $C_{14}H_{19}O_3$ $(M+H)^+$: 235.1334, Found: 235.1331.

***cis* methyl 2-(4-phenyltetrahydro-2H-pyran-2-yl)acetate** (***cis*-24**). Colourless oil. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.20-7.35 (m, 5H), 4.11 (dt, *J* = 6.1, 3.4 Hz, 1H) 3.90 (dddd, *J* = 10.4, 7.9, 5.2, 2.1 Hz, 1H), 3.70 (s, 3H), 3.60 (m, 1H), 2.78-2.86 (m, 1H), 2.60 (dd, *J* = 15.2, 7.9 Hz, 1H), 2.45 (dd, *J* = 15.2, 5.2 Hz, 1H), 1.88-1.91 (m, 2H), 1.76 (m, 2H), 1.49 (q, *J* = 12.5 Hz, 1H) ppm; $^{13}$C{H} NMR (100 MHz, $CDCl_3$): δ 33.3, 39.2, 41.5, 41.7, 51.9, 68.5, 74.4, 126.6, 126.9, 128.7, 145.5, 171.9 ppm; FTIR: 1730, 1603, 1495, 1435, 1381, 1310, 1283, 1202, 1155, 1126, 1084, 1007, 760, 700, 532 cm$^{-1}$; HRMS (ESI-TOF) m/z: Calculated for $C_{14}H_{19}O_3$ $(M+H)^+$: 235.1334, Found: 235.1329.

***cis* methyl 2-(3-phenyltetrahydro-2H-pyran-2-yl)acetate** (***cis*-25**). Yellow oil. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.41-7.42 (m, 2H), 7.20-7.32 (m, 3H), 4.25 (ddd, *J* = 9.3, 4.5, 3.5 Hz, 1H), 4.04-4.10 (m, 1H), 3.62-3.68 (m, 2H), 3.63 (s, 3H), 2.92 (q, *J* = 4.4 Hz, 1H), 2.56 (dd, *J* = 15.6, 9.3 Hz, 1H), 2.15 (dd, *J* = 15.6, 4.5 Hz, 1H), 1.99-2.05 (m, 1H), 1.84-1.92 (m, 2H), 1.41-1.48 (m, 1H) ppm; $^{13}$C{H} NMR (100 MHz, $CDCl_3$): δ 21.7, 29.2, 37.8, 43.4, 51.8, 67.4, 76.4, 126.5, 128.4, 129.4, 142.1, 172.4 ppm; FTIR: 1748, 1645, 1602, 1495, 1435, 1371, 1317, 1258, 1192, 1167, 1082, 1003, 762, 706, 488 cm$^{-1}$; HRMS (ESI-TOF) m/z: Calculated for $C_{14}H_{19}O_3$ $(M+H)^+$: 235.1334, Found: 235.1332.

***trans* methyl 2-(3-phenyltetrahydro-2H-pyran-2-yl)acetate** (***trans*-25**). Yellow oil. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.17-7-32 (m, 3H), 7.26-7.32 (m, 2H), 4.04-4.08 (m, 1H), 3.92 (ddd, *J* = 10.0, 8.9, 3.5 Hz, 1H), 3.58-3.61 (m, 1H), 2.52 (td, *J* = 10.0, 4.1 Hz, 1H), 2.30 (dd, *J* = 15.2, 8.9 Hz, 1H), 2.23 (dd, *J* = 15.2, 3.5 Hz, 1H), 1.99-2.00 (m, 1H), 1.66-1.83 (m, 3H) ppm; $^{13}$C{H} NMR (100 MHz, $CDCl_3$): δ 26.4, 32.3, 39.5, 48.6, 51.7, 68.7, 79.1, 127.0, 127.9, 128.9, 142.7, 171.3 ppm; FTIR: 1742, 1634, 1493, 1435 1375, 1290, 1204, 1163, 1107, 1078, 1047, 760, 703, 530 cm$^{-1}$; HRMS (ESI-TOF) m/z: Calculated for $C_{14}H_{19}O_3$ $(M+H)^+$: 235.1334, Found: 235.1345.

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[11] The *trans* and *cis* diastereomers were found to be an inseparable mixture, but the *trans* isomer could be obtained in pure form by driving the isomerisation to full completion at reflux.