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Sequential hydroformylation/aldol reactions: versatile and controllable access to functionalised carbocycles from unsaturated carbonyl compounds

Mark D. Keränen, Kinga Kot, Christoph Hollmann and Peter Eilbracht*
Fachbereich Chemie, Organische Chemie I, Universität Dortmund, Otto-Hahn-Str. 6, D-44227 Dortmund, Germany. E-mail: peter.eilbracht@udo.edu; Fax: +49(0)231 755 5363; Tel: +49(0)231 755 3857

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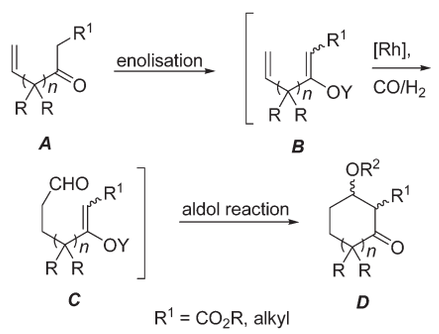
Three different modes of hydroformylation/aldol reaction sequences involving either acid-catalysed aldol reactions, Mukaiyama aldol addition of pre-formed enolsilanes or aldol addition of *in situ* generated boron enolates can be applied to unsaturated ketones and ketoesters to afford the corresponding carbocyclic aldol adducts in good yields proceeding through the intermediate activated ketoaldehydes. In selected cases, complimentary, synthetically useful diastereoselectivities were observed in the products.

Introduction

The formation of carbocyclic rings possessing functionality lending itself to further manipulation *via* subsequent transformations is a fundamental goal in organic chemistry and a process of universal importance in organic synthesis. Countless applications of such methodologies are found in the multitudes of cyclic/polycyclic natural products possessing these structural moieties. Thus, improved strategies allowing for the straightforward construction of these useful compounds are constantly in demand.

Hydroformylation, an industrially important method for much of the last century, has more recently emerged in a variety of applications towards the total synthesis of natural products and related compounds.[1] Several examples combining the generation of a reactive aldehyde *via* hydroformylation with subsequent C–C bond-forming reactions have also been reported.[2] In the specific context of intramolecular aldol reactions coupled to hydroformylation processes, a major advantage lies in the fact that since an aldehyde can be generated from its olefin precursor in the presence of a pre-formed enolate equivalent, the neccessity of employing more laborious strategies[3] where the aldehyde must be protected and deprotected is eliminated. In these sequences, unsaturated carbonyl compounds of type **A** are first exposed to reaction conditions that activate the carbonyl group for aldol addition, generating reactive intermediates of type **B** which then undergo hydroformylation to give aldol precursors of type **C**, reacting to produce substituted carbocycles of type **D** (Scheme 1).

In recent studies, we have reported examples of the intramolecular hydroformylation/aldol reactions of selected unsaturated ketones and their trialkylsilyl enol ethers, which afforded the corresponding cyclic aldol adducts in good yields.[4] We have also developed a new, mild enolboration/hydroformylation/aldol addition cascade reaction that allows for the regio- and diastereoselective construction of carbocycles bearing highly-functionalised quaternary carbon centers.[5] Expanding upon these findings, we describe herein a study which determines the scope and limitations of the methods of activation towards aldol reactions under hydroformylation conditions. Investigated are the methods of hydroformylation in the presence of mild acid-catalysis (method A), sequential hydroformylation/Mukaiyama aldol additions (method B) and sequential enolboration/hydroformylation/aldol addition (method C). In this study, we applied these various modes of hydroformylation/aldol reaction sequences with the goal of obtaining carbocycles with varying functionality starting from easily obtainable acyclic olefins, while at the same time desiring to learn more about the various methods in the context of obtaining high levels of diastereoselectivity in the aldol addition step.



Scheme 1 Activation towards aldol addition under hydroformylation conditions.

Results and discussion

The unsaturated ketoesters and ketones used in this study, ethyl 4,4-dimethyl-3-oxo-hex-5-enoate (**1**),[6] ethyl 2-methyl-3-oxo-hex-5-enoate (**3**),[7] 3,3-dimethyl-4-penten-2-one (**4**)[8] and 4,4-dimethyl-5-hexen-3-one (**5**),[9] were obtained *via* literature procedures. The *E*(O)-enolsilanes ethyl 4,4-dimethyl-3-trimethylsilanoxy-hexa-2,5-dienoate (**2**) and (1-ethylidene-2,2-dimethyl–but-3-enyloxy)-*tert*-butyl dimethylsilane (**6**) were stereoselectively synthesised *via* treatment with LDA and the appropriate trialkylsilyl chloride in 80% and 38% yield, respectively. Investigations began on the sequential hydroformylation/aldol reactions of the unsaturated β-ketoester **1** and its TMS-silyl enol ether **2**.

Following the application of the three hydroformylation/aldol reaction sequences mentioned above to compounds **1** and **2**, a unique result was obtained for each sequence used. In the hydroformylation/acid-catalyzed sequence (method A), ketoester **1** underwent a Knoevenagel condensation, and the resulting enone was hydrogenated to give ethyl 3,3-dimethyl-2-oxo-cyclohexanecarboxylate (**1a**)[10] in 72% yield as an approximately 2:1 ratio of *enol*- and *keto*-tautomers in $CDCl_3$.(Scheme 2).

To extend these results, we attempted to retain oxygen functionality in the product by suppressing the elimination of water and the subsequent hydrogenation that occurs in the acid-catalysed scenario, which would result in the production

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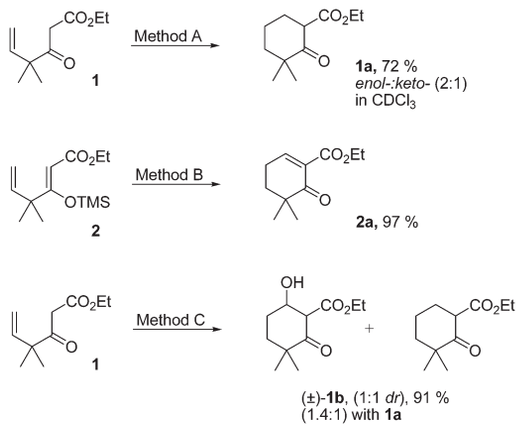
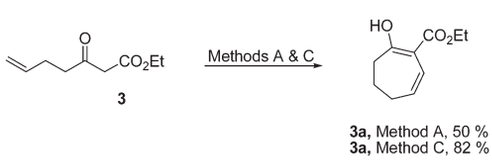


Scheme 2 Hydroformylation/aldol sequences of β-ketoester **1** and enolsilane **2**. Conditions method A: 0.9 mol% $[Rh(cod)Cl]_2$, 10.0 mol% *p*-TsOH, CH_2Cl_2, 60 bar CO/H_2, 80 °C, 20 h. Method B: 0.9 mol% $[Rh(cod)Cl]_2$, CH_2Cl_2, 60 bar CO/H_2, 80 °C, 20 h. Method C: 1.05 eq. $(cy\text{-}hex)_2BCl$, 1.05 eq. Et_3N, 0 °C, 0.9 mol% $Rh(CO)_2(acac)$, 60 bar CO/H_2, 80 °C, 20 h.

of diastereomeric aldol adducts. We began to explore the possibility for stereoselective aldol addition in this reaction sequence by investigating the Rh-catalyzed Mukaiyama aldol reaction[11] under hydroformylation conditions. Application of method B to enolsilane **2** produced a significant result as the *non-hydrogenated* Knoevenagel product ethyl 5,5-dimethyl-6-oxo-cyclohex-1-enecarboxylate (**2a**) was produced in nearly quantitative yield. It is postulated that the neutral conditions under which the hydroformylation/Mukaiyama aldol takes place do not sufficiently activate the Rh catalyst or the substrate to allow hydrogenation to occur. In an attempt to perform the reaction under other conditions to suppress the elimination of water, ketoester **1** was exposed to the enolboration/hydroformylation/aldol addition conditions. Upon oxidative workup, a 1.4 : 1 mixture of the unstable ethyl 6-hydroxy-3,3-dimethyl-2-oxo-cyclohexanecarboxylate (**1b**)[12] and **1a** was produced in 91% yield. Although not completely selective for one product, the synthesis of **1b** further illustrates the mild conditions under which the cascade reaction proceeds, allowing for the production of a sensitive functional group not obtainable *via* the other methods of activation.

The reactivity of β-ketoesters towards aldol addition using methods A and C was again studied using ketoester **3**. Upon exposure to both methods, the cyclic diene ethyl 2-hydroxy-cyclohepta-1,6-dienecarboxylate (**3a**)[13] was produced in 50% and 82% yields, respectively (Scheme 3).

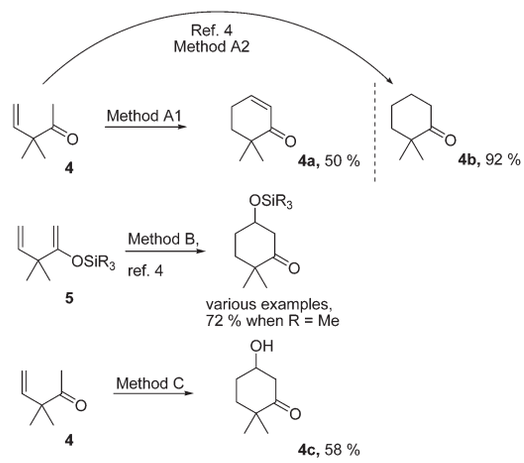


Scheme 3 Hydroformylation/aldol reactions of β-ketoester **3**. Conditions method A: 0.6 mol% $Rh(CO)_2(acac)$, 2.4 mol% BIPHEPHOS, 10.0 mol% *p*-TsOH, CH_2Cl_2, 20 bar CO/H_2, 60 °C, 20 h. Method C: 1.05 eq. $(cy\text{-}hex)_2BCl$, 1.05 eq. Et_3N, 0 °C, 0.9 mol% $Rh(CO)_2(acac)$, 1.8 mol% XANTPHOS, 60 bar CO/H_2, 80 °C, 20 h.

With this result, it was postulated that the elimination of water was a driving force in the aldol reactions of such ketoesters, that a change to a less-activated ketone substrate would be a more effective means by which to render the elimination of water less favourable in order to investigate the stereochemical nuances of each particular reaction sequence. In order to test this hypothesis, the reactions of ketones **4**, **6** and TBS-enolsilane **7** were investigated.

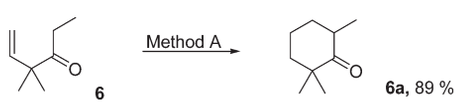
Having already reported[4] the reactions of ketone **4** using method A and its trialkylsilyl enol ethers **5** using method B, where in the acid-catalysed scenario longer reaction times result in the production of 2,2-dimethylcyclohexanone (**4b**)[15] in 92% yield, it was found that 6,6-dimethylcyclohex-2-enone (**4a**)[14] can be synthesized in 50% yield by employing shorter reaction times. The result suggests that for this substrate the hydrogenation step proceeds slowly in the presence of the rhodium hydroformylation catalyst.

It now remained to test whether or not our newly-reported cascade reaction sequence (method C) was compatible with ketones before we studied the stereochemical consequences of the three methods. Isolation of the alcohol 5-hydroxy-2,2-dimethyl–cyclohexanone (**4c**) in 58% yield showed indeed that ketones are a suitable substrate for the reaction cascade, and that once again, very sensitive functional groups can be produced without the observance of unwanted side reactions such as elimination or retro aldol sequences (Scheme 4).



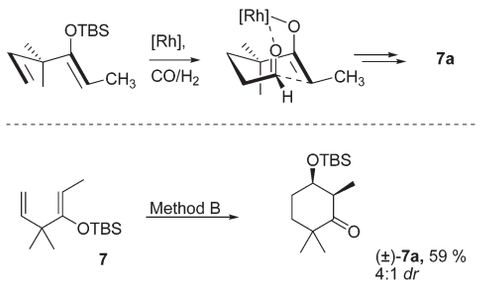
Scheme 4 Hydroformylation/aldol sequences of ketone **4** and enolsilanes **5**. Conditions method A1: 0.5 mol% $[Rh(cod)Cl]_2$, 10.0 mol% *p*-TsOH, CH_2Cl_2, 80 bar CO/H_2, 100 °C, 20 h. Method A2: 0.5 mol% $[Rh(cod)Cl]_2$, 10.0 mol% *p*-TsOH, CH_2Cl_2, 80 bar CO/H_2, 100 °C, 66 h. Method B: 0.9 mol% $[Rh(cod)Cl]_2$, CH_2Cl_2, 80 bar CO/H_2, 90 °C, 20 h. Method C: 1.05 eq. $(cy\text{-}hex)_2BCl$, 1.05 eq. Et_3N, 0 °C, 0.9 mol% $Rh(CO)_2(acac)$, 60 bar CO/H_2, 80 °C, 20 h.

Encouraged by these results, studies continued with **6**, where the introduction of the methyl group in the starting material will allow for the production of diastereomeric aldol adducts when the elimination of water is stopped, as was demonstrated above *via* the use of methods B and C in the case of the unsubstituted substrates. Before this was carried out, a first experiment was performed with ketone **6** using method A. Following hydroformylation in the presence of 0.5 mol% $[Rh(cod)Cl]_2$[16] and 10 mol% *p*-TsOH, 2,2,6-trimethylcyclohexanone (**6a**)[17] was obtained as the sole product in 89% yield (Scheme 5).



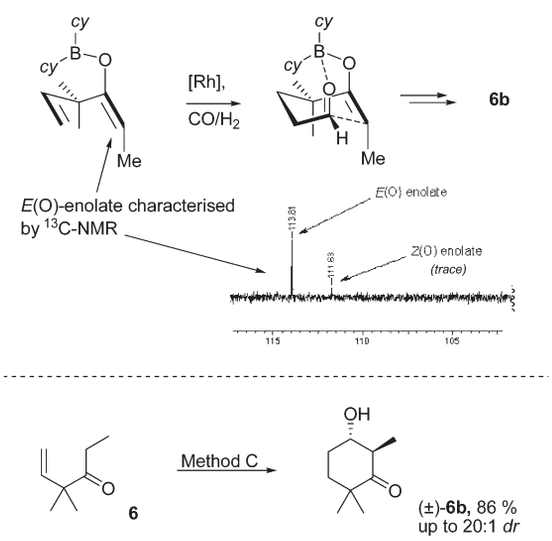
Scheme 5 Sequential hydroformylation/aldol reaction of ketone **6**. Conditions method A: 0.5 mol% $[Rh(cod)Cl]_2$, 10.0 mol% *p*-TsOH, CH_2Cl_2, 80 bar CO/H_2, 100 °C, 66 h.

A study of the stereoselectivity of the sequential hydroformylation/Mukaiyama aldol reaction was carried out next. It was envisioned that after transmetalation of a preformed *Z*(O)-enolsilane, a Rh-enolate would be generated which then undergoes a chelation-controlled aldol addition with the aldehyde generated from the olefin unit.[18] The *Z*(O)-TBS-silyl enol ether of ketone **6**, (1-ethylidene-2,2-dimethyl-but-3-enyloxy)-*tert*-butyl dimethylsilane (**7**) proved to be the most suitable substrate, reacting to give *cis*-5-(*tert*-butyl-dimethylsilanoxy)-2,2,6-trimethylcyclohexanone (**7a**) in 59% and 4 : 1 dr for the *cis*-isomer as detected by NMR (Scheme 6). A further highlight of this method is that 0.9 mol% Rh is sufficient to catalyse both the hydroformylation and the aldol addition.



Scheme 6 Sequential hydroformylation/aldol reaction of TBS-enolsilane **7**. Conditions Method B: 0.9 mol % $[Rh(cod)Cl]_2$, CH_2Cl_2, 60 bar CO/H_2, 80 °C, 20 h.

Bolstered by this result, studies continued once again with ketone **6**, where it was imagined that a stereoselectively *in situ*-generated *E*(O)-boron enolate[19] of ketone **6** could undergo chelation-controlled aldol addition after hydroformylation, thus allowing for the stereoselective synthesis of both *cis*- and *trans*-substituted cyclohexanones in conjunction with the Mukaiyama variant. ^{13}C-NMR experiments used to determine a nearly exclusive *E*(O)-configuration of the *in situ* generated enolate[20] at 0 °C were used along with ^{1}H-NMR coupling constants of the product to confirm the production of (±)-*trans*-5-hydroxy-2,2,6-trimethylcyclohexanone (**6b**) in excellent diastereoselectivity (up to 20 : 1 *dr*) and 86% yield (Scheme 7).



Scheme 7 Highly diastereoselective sequential enolboration/ hydroformylation/aldol addition reaction of ketone **6**. Conditions method C: 1.05 eq. $(cy\text{-}hex)_2BCl$, 1.05 eq. Et_3N, 0 °C, 0.9 mol% $Rh(CO)_2(acac)$, 60 bar CO/H_2, 80 °C, 20 h.

Conclusion

In summary, we herein report the latest developments in our continuing exploration of stereoselective hydroformylation/aldol addition reaction sequences, and their application to the one-pot synthesis of various functionalised carbocyclic compounds. In addition to yielding the desired carbocycles through the use of three different sets of conditions, two cases result in the diastereoselective production of both *cis*- and *trans*-C5/C6-substituted cyclohexanones in high yields and selectivities, which is a substantial improvement over the previously reported diastereoselectivites available by use of these methods. These three complimentary strategies provide a significant advancement over other available methods of carbocyclic ring synthesis in that they offer rapid, one-pot access to the products from readily-available acyclic starting materials, without the use of otherwise necessary protection–deprotection strategies.

Experimental

All air-sensitive reactions were performed under an argon atmosphere using distilled solvents where required. Triethylamine (Et_3N) was distilled from calcium hydride (CaH_2). All other reagents were commercially purchased and used without further purification. ^{1}H and ^{13}C NMR spectra were measured using Bruker DRX 400 and 500 MHz instruments using $CDCl_3$ as the solvent and internal standard. Hydroformylation/aldol reactions were carried out in autoclaves, 250 mL PTFE insert or 70 mL stainless steel, with specially designed heating and stirring mantles.

Procedure for hydroformylation/acid-catalysed aldol reactions (method A)

To a stirring autoclave containing 10 mL of absolute CH_2Cl_2 was added the β,γ-unsaturated carbonyl compound in approx. 1 mL of solvent. The mixture is stirred as 5–10% *p*-TsOH and 0.5–1.0 mol% hydroformylation catalyst is added. The autoclave is then sealed and subjected to the required temperature and pressures of CO and H_2. **CAUTION!** When the reaction is complete, the autoclave is cooled to RT, depressurised and flushed once with argon. The crude reaction mixture is removed and filtered with ether through a small plug of neutral alumina. The solvent is then stripped and the residue is subjected to further purification *via* Kugelrohr distillation or column chromatography when necessary.

Procedure for hydroformylation/Mukaiyama aldol reactions (method B)

To a stirring autoclave containing 10 mL of absolute CH_2Cl_2 was added the enolsilane in approx. 1 mL of solvent. The mixture is stirred as 0.9 mol% of $Rh(CO)_2(acac)$ is added. The autoclave is then sealed and subjected to the required temperature and pressures of CO and H_2. When the reaction is complete, the autoclave is cooled to RT, depressurised and flushed once with argon. The crude reaction mixture is removed and filtered with ether through a small plug of neutral alumina. The solvent is then stripped and the residue is subjected to further purification *via* Kugelrohr distillation or column chromatography when necessary.

Procedure for sequential enolboration/hydroformylation/ aldol addition (method C)[5]

Et_3N (1.05 eq. to carbonyl compound) was pre-complexed under an argon atmosphere with $(cy\text{-}hex)_2BCl$ (1.05 eq.) in dry CH_2Cl_2 (5 mL) at 0 °C for 15 min. The unsaturated carbonyl compound in approx. 1 mL of solvent was then added slowly *via* syringe and the enolboration was allowed to stir for an additional 30 min. The mixture was simply transferred into the autoclave containing 0.9 mol% $Rh(CO)_2(acac)$ and 10–15 mL of solvent. The autoclave was then pressurised to 60 bar with equal pressures of CO and H_2 and heated overnight to 80 °C. Upon cooling the autoclave to RT, the reaction mixture was removed and concentrated under reduced pressure. Enough MeOH was added to dissolve the solid residue (~25 mL) along with 2 mL of conc. pH 7 phosphate buffer and 1 mL of 30% H_2O_2, and the reaction was allowed to stir overnight before being extracted with ether (100 mL), washed with sat. aq. $NaHCO_3$ (1 × 75 mL), dried and concentrated prior to further purification when necessary *via* flash chromatography or Kugelrohr distillation.

Ethyl 4,4-dimethyl-3-oxo-hex-5-enoate 1.

A mixture of zinc powder (19.6 g, 0.3 mol), $AlCl_3$ (4.0 g, 30.0 mmol) and cyano ethyl acetate (10.6 mL, 90.0 mmol) was stirred in 200.0 mL of dry THF at 0 °C. After 15 min a solution of prenyl bromide (11.5 mL, 0.1 mol) in 15 mL THF was added dropwise. After addition was complete, the reaction was left to warm to RT and was stirred overnight, when 200 mL of 2 M HCl was added to the reaction mixture and stirring was continued for another 15 min. The reaction was filtered and

washed with sat. aq. $NaHCO_3$ (3 × 100 mL) and brine (100 mL) before being dried, concentrated and purified by column chromatography (5 : 1 CH_2Cl_2–hexane) to give 11.2 g (61%) of 1 as a pale yellow oil. All spectra matched those reported in the literature.[6]

Ethyl 2-oxo-3,3-dimethyl-cyclohexanecarboxylate 1a.

Obtained from ethyl 4,4-dimethyl-3-oxo-hex-5-enoate (1) (0.46 g, 2.5 mmol) and method A using 0.9 mol% (6 mg) $[Rh(cod)Cl]_2$, 47.0 mg (10 mol %) *p*-TsOH, 80 bar CO/H_2, 80 °C for 24 h as a 2 : 1 mixture of *enol–keto* tautomers in 72% as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 3H, CH_3); 1.19 (s, 3H, CH_3); 1.28 (t, J = 8 Hz, 3H, CH_3); 1.60–1.79 (m, 6H, 2 × CH_2); 3.58 (dd, J = 8, 12 Hz, 1H, CH); 4.20 (q, J = 8 Hz, 2H, OCH_2R). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.3, 20.0, 25.4, 26.9, 36.2, 45.7, 53.8, 60.9, 173.3, 210.5. FTIR ($CDCl_3$) 2964, 2868, 1743, 1711, 1610, 1312, 838. ESI-MS *m*/*z* 198.2 $[M]^+$. HR-EIMS anal. calc. for $C_{11}H_{18}O$ $[M]^+$: 198.1256; anal. found: 198.1252.

Ethyl 6-hydroxy-3,3-dimethyl-2-oxo-cyclohexanecarboxylate 1b.

Obtained from 1 (200 mg, 1.08 mmol) using method C with 4.0 mg $Rh(CO)_2$(acac), 0.16 mL (1.13 mmol) Et_3N and 1.13 mL (1.13 mmol) (*cy*-hex)$_2$BCl in CH_2Cl_2 at 80 bar and 90 °C for 20 h. Workup as described above resulted in 211 mg (0.98 mmol) 1b (1 : 1 *dr*) in 91% yield as a clear yellow oil in a 1.4 : 1 ratio with 1a.

Diastereoisomer 1.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.19 (t, J = 8 Hz, 3H, CH_3); 1.26 (m, 3H, CH_3); 1.46 (m, 3H, CH_3); 1.52 (m, 2H, CH_2); 1.81 (m, 2H, CH_2); 3.53 (m, 2H, CH_2); 4.12 (q, J = 8 Hz, 2H, OCH_2R). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.0, 24.0, 24.7, 25.0, 28.0, 45.8, 53.7, 60.7, 70.1, 173.1, 200.1.

Diastereoisomer 2.

^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.9 (*C*H$_3$), 60.0 (*C*H$_2$), 176.9 (*C*O$_2$R). FTIR (neat): 3400 (broad), 2932, 2856, 1731, 1650, 1610, 1454, 1254, 1030, 827. ESI-MS *m*/*z* 214.1 $[M]^+$; *2m*/*z* 429.1 $[2M + H]^+$.

Ethyl 4,4-dimethyl-3-trimethylsilanyloxy-hexa-2,5-dienoate 2

To a stirred prepared solution of LDA (60.0 mmol) under argon in THF at −78 °C was added ethyl 4,4-dimethyl-3-oxo-hex-5-enoate (**1**) (9.2 g, 50.0 mmol) in 2 mL THF. This solution was stirred for 1 h before TMSCl (11 mL, 87.0 mmol) was added. After 10 min the cooling bath was removed and the reaction was allowed to warm with stirring overnight to RT. The solvent was removed and the residue was taken up in hexanes and filtered through alumina to give **2** (10.2 g, 40 mmol) as a yellow oil in 80% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.25 (s, 9H, 3 × CH_3); 1.17 (s, 6H, 2 × CH_3); 1.22 (t, J = 8 Hz, 3H, CH_3); 4.08 (q, J = 8 Hz, 2H, OCH_2R); 5.05 (dd, J = 8, 16 Hz, 2H, RHC=CH_2); 5.21 (s, 1H, R_2C=C*H*CO$_2$Et); 5.85 (dd, J = 8, 16 Hz, 1H, R*H*C=CH$_2$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 1.16, 14.39, 25.10, 44.39, 59.01, 96.59, 112.79, 144.25, 166.11, 173.23. FTIR (neat): 2972, 1717, 1617, 1250, 1175, 846. HR-EIMS anal. calc. for $C_{13}H_{24}O_3Si$: 256.1495; anal. found: 256.1482.

Ethyl 5,5-dimethyl-6-oxo-cyclohex-1-enecarboxylate 2a

Obtained from **2** (500 mg, 2.06 mmol) and method B using 10.0 mg (1.0 mol%) $[Rh(cod)Cl]_2$, 40 bar CO/H_2 and 60 °C for 48 h giving **2a** in 97% (365 mg, 2.00 mmol). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 6H, 2 × CH_3); 1.26 (t, J = 7.5 Hz, 3H, CH_3); 1.82 (t, J = 5 Hz, 2H, CH_2); 2.47 (dt, J = 5, 7.5 Hz, 2H, CH_2); 4.19 (q, J = 7.5 Hz, 2H, OCH_2R); 7.48 (t, J = 7.5 Hz, 1H, R_2C=C*H*R). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 15.6, 24.7, 24.9, 25.2, 37.0, 43.3, 62.5, 133.2, 155.1, 166.7, 201.5. FTIR (neat): 2995, 2898, 1750, 1360, 1040. HR-FABMS anal. calc. for $C_{11}H_{17}O_3$ $[M + H]^+$: 197.1178; anal. found: 197.1205.

Ethyl 2-methyl-3-oxo-hept-6-enoate 3

To a stirring mixture of 1.20 g (32.0 mmol) 60% NaH in 100 mL dry THF cooled to 0 °C was added 3.90 g (30 mmol) ethyl 3-oxo-butyrate *via* syringe. When addition was complete, the mixture was stirred for 30 min at 0 °C before 11.7 mL (50 mmol) of *n*-BuLi (2.5 M in hexane) was added over 10 min *via* syringe. The mixture was stirred for another 10 min before allyl bromide (3.99 g, 33 mmol) was added and the mixture was allowed to warm to RT while stirring. The reaction was then quenched *via* the slow addition of 100 mL sat. aq. NH_4Cl solution, extracted with Et_2O (1 × 50 mL) and washed with brine before being dried, concentrated and purified by Kugelrohr distillation to give 3.9 g ethyl 3-oxo-hept-6-enoate (**3**) (24.7 mmol, 82%) as a pungent-smelling, light yellow oil which was immediately taken on to the subsequent methylation reaction without purification. All spectral data matched those reported in the literature.[7]

Ethyl-2-hydroxy-cyclohepta-1,6-dienecarboxylate (3a) *via* method A

Obtained from **3** (0.85 g, 5.0 mmol) using method A with 8.0 mg $Rh(CO)_2$(acac), 94.0 mg BIPHEPHOS and 29 mg *p*-TsOH in 15 mL CH_2Cl_2 at 20 bar and 60 °C for 20 h. Workup as described above resulted in **3b** (0.46 g, 2.5 mmol) in 50% yield as a pale yellow oil after column chromatography (*n*-hexane–MTBE = 6 : 1). All spectra were identical to those reported in the literature.[13] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J = 7.2 Hz, 3H, CH_3); 1.96 (m, 2H, CH_2); 2.24 (m, 2H, CH_2); 2.48 (m, 2H, CH_2); 4.22 (q, J = 7.2 Hz, 2H, OCH_2R); 5.62 (dt, J = 4.9, 12.2 Hz, 1H, RHC=C*H*R); 6.19 (dt, J = 1.9, 12.2 Hz, 1H, R*H*C=CHR); 13.15 (s, 1H, R2C=C(O*H*)R). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.2, 26.3, 30.0, 34.9, 60.7, 99.3, 121.3, 126.6, 172.5, 179.1. FTIR (neat): 3200 (broad), 3036, 2960, 1640, 1379, 1242, 1057 cm^{-1}. GC-MS (EI, 70 eV): *m*/*z* (%) = 183 (M^+ + 1, 100); 154 (5); 137 (32); 126 (3); 108 (12); 81 (18); 67 (10).

Ethyl-2-hydroxy-cyclohepta-1,6-dienecarboxylate (3a) *via* method C

Obtained from **3** (170.2 mg, 1.5 mmol) using method C with 3.0 mg $Rh(CO)_2$(acac), 12.0 mg XANTPHOS, 0.23 mL (1.5 mmol) Et_3N and 1.2 mL (1.2 mmol) (*cy*-hex)$_2$BCl solution in CH_2Cl_2 at 80 bar and 90 °C for 16 h. Workup as described above resulted in **4b** (220.0 mg, 1.2 mmol) in 83% yield as a pale yellow oil needing no further purification. All spectra were identical to those reported in the literature[13] and for the previous trial with method A.

3,3-Dimethyl-pent-4-en-2-one 4

In a two-necked round-bottom flask containing 200 mL CH_2Cl_2 cooled to 0 °C was added $AlCl_3$ (13.3 g, 0.10 mol) followed by acetyl chloride (8.6 g, 0.11 mol) slowly *via* syringe. After stirring for 30 min the mixture was taken up in an addition funnel and dropped into a stirring mixture of trimethylprenyl silane (14.3 g, 0.10 mol) in 100 mL CH_2Cl_2 cooled to −60 °C. After addition was complete, the mixture was stirred for an additional 10 min before being poured over a mixture of ice and 100 mL sat. aq. NH_4Cl solution. The mixture was extracted with CH_2Cl_2 before being dried, concentrated and purified by Kugelrohr distillation (70 °C at 200 mbar) to give 8.7 g (78.0 mmol) of 3,3-dimethyl-pent-4-en-2-one (**4**) as a colourless oil in 78% yield. All spectra matched those present in the literature.[8]

6,6-Dimethyl-cyclohex-2-enone 4a

Obtained from **4** (560.0 mg, 5.0 mmol) using method A with 12.0 mg $[Rh(cod)Cl]_2$, 10.0 mol% *p*-TsOH and 15 mL CH_2Cl_2 at

80 bar and 100 °C for 20 h. Workup as described above resulted in **4a** (310.0 mg, 2.5 mmol) in 50% yield as a near-colourless oil. All spectra matched those present in the literature.[14] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 6H, 2 × C*H*$_3$); 1.80 (t, J = 6.1 Hz, 2H, CH_2); 2.35 (ddt, J = 2.0, 4.0, 6.1 Hz, 2H, CH_2); 5.88 (dt, J = 2.0, 10.0 Hz, 1H, R*H*C=CHR); 6.84 (dt, 4.0, 10.0 Hz, 1H, RHC=C*H*R). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 23.2, 24.0, 36.1, 41.3, 128.2, 148.6, 204.5. FTIR ($CDCl_3$): 3033, 2964, 2925, 2870, 1682, 1450, 1131. GC-MS (EI, 70 eV): *m*/*z* (%) = 125 (M^+ + 1, 45); 108 (3); 95 (5); 68 (100); 53 (5).

5-Hydroxy-2,2-dimethyl-cyclohexanone 4c

Obtained from **4** (200 mg, 1.8 mmol) using method C with 4.0 mg $[Rh(cod)Cl]_2$, 0.26 mL (1.9 mmol) Et_3N and 1.89 mL (1.9 mmol) (*cy*-hex)$_2$BCl solution in CH_2Cl_2 at 60 bar and 90 °C for 16 h. Workup as described above resulted in **4b** (148 mg, 1.04 mmol) in 58% yield as a pale-yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 3H, C*H*$_3$); 1.56 (s, 3H, C*H*$_3$); 1.69 (m, 4H, 2 × CH_2); 2.10 (d, J = 5 Hz, 2H, α-CH_2); 3.58 (m, 1H, R_2C*H*(OH)). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 24.0, 24.1, 25.3, 26.5, 36.6, 47.2, 70.2, 214.4. FTIR ($CDCl_3$): 3466 (broad), 2933, 1702, 1451, 1097, 909. Anal. calc. for $C_8H_{14}O_2$: C, 67.6; H, 9.9; anal. found: C, 67.8; H, 10.1.

4,4-Dimethyl-hex-5-en-3-one 6

A two-necked 250 mL round-bottom flask containing a stirring mixture of 40 mL sat. aq. NH_4Cl solution and 8 mL of THF was maintained at RT using a water bath as prenyl bromide (5.8 g, 38.9 mmol) and propionaldehyde (3.0 mL, 52.0 mmol) were added to the mixture. With continued vigorous stirring, Zn powder (4.0 g, 62.0 mmol) was slowly added portion-wise to the mixture. The mixture heated up considerably upon addition of the metal, and after addition was complete the reaction was stirred for an additional 2 h, upon which the mixture was extracted with ether, dried and concentrated to give the crude 4,4-dimethyl-hex-5-en-3-ol, which was taken up in ether and stirred at RT as 30 mL of Jones reagent was dropped to the mixture over 30 min. After addition, the mixture was stirred for an additional 2 h before being extracted with ether and washed repeatedly with sat. aq. $NaHCO_3$ solution. The organic layer was separated, dried and concentrated to give 3.5 g (28 mmol) 4,4-dimethyl-hex-5-en-3-one (**6**) in 72% yield as a pale yellow oil which was used in future reactions without further purification. All spectra matched those reported in the literature.[9]

2,2,6-Trimethylcyclohexanone 6a

Obtained from 4,4-dimethyl-hex-5-en-3-one (**6**) (630.0 mg, 5.0 mmol) and method A using 12 mg (0.5 mol%) $[Rh(cod)Cl]_2$ and 95.0 mg (10 mol%) *p*-TsOH affording **6a** in 89% (620.0 mg, 4.5 mmol) after column chromatography (20 : 1 *n*-hexane–MTBE). All spectra matched those reported in the literature.[17]

5-Hydroxy-2,2,6-trimethyl-cyclohexanone 6b

Obtained from 4,4-dimethyl-hex-5-en-3-one (**6**) (202.0 mg, 1.6 mmol) using method C with 4 mg $[Rh(cod)Cl]_2$, 0.23 mL (1.7 mmol) Et_3N and 1.7 mL (1.7 mmol) (*cy*-hex)$_2$BCl solution in CH_2Cl_2 at 60 bar and 90 °C for 16 h. Workup as described above resulted in 86% yield of **6b** (215.0 mg, 1.37 mmol) in up to 20 : 1 *dr* as a pale yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.07 (d, J = 8 Hz, 3H, C*H*$_3$); 1.18–1.27 (m, 6H, 2 × C*H*$_3$); 1.53 (m, 2H, CH_2); 1.85 (m, 2H, CH_2); 2.45 (dq, J = 3.5, 8 Hz, 1H, α-C*H*); 3.57 (m, 1H, R_2C*H*(OH)). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 8.0, 24.0, 24.2, 24.4, 29.9, 43.7, 46.0, 70.3, 216.7. FTIR (neat): 3399 (broad), 2934, 1704, 1452, 1100, 972. ESI-MS $[M + H]^+$: 157.1. HR-FABMS anal. calc. for $C_9H_{16}O_2$ $[M]^+$: 156.1150; anal. found: 157.1220.

***tert*-Butyl-(1-ethylidene-2,2-dimethyl–but-3-enyloxy)-dimethylsilane 7**

To a stirred prepared solution of LDA (8.0 mmol) under argon in THF at −78 °C was added 4,4-dimethyl-hex-5-en-3-one (**6**) (500.0 mg, 4.0 mmol) in 1 mL THF. This solution was stirred for 30 min before HMPA (2 mL) and TBSCl (4.1 mmol) were added. After 10 min the cooling bath was removed and the reaction was allowed to warm with stirring to RT. After stirring an additional 2 h, the solvent was removed and the residue was filtered through a small plug of neutral alumina with *n*-hexane to give **7** as a transparent light yellow oil in 38% yield (376 mg, 1.5 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) δ −0.15 (s, 6H, 2 × C*H*$_3$); 0.96 (s, 9H, *t-Bu*); 1.14 (s, 6H, 2 × C*H*$_3$); 1.52 (d, J = 8 Hz, 3H, C*H*$_3$); 4.60 (q, J = 8 Hz, 1H, R2C=C*H*CH$_3$); 4.95 (dd, J = 20, 24 Hz, 2H, RHC=CH_2); 5.89 (dd, J = 12, 20 Hz, 1H, R*H*C=CH$_2$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ −2.81, 11.76, 19.11, 26.08, 26.44, 42.89, 98.94, 111.00, 146.88, 156.73. FTIR (neat): 2960, 2930, 2858, 1662, 1472, 1320, 1076, 837. HR-EIMS anal. calc. for $C_{14}H_{28}OSi$ $[M]^+$: 240.1909; anal. found: 240.1900.

5-(*tert*-Butyl–dimethyl–silanyloxy)-2,2,6-trimethyl-cyclohexanone 7a

Obtained from *tert*-butyl-(1-ethylidene-2,2-dimethyl-but-3-enyloxy)-dimethylsilane (**7**) (100.0 mg, 0.4 mmol) and method B using 3 mg $Rh(CO)_2$acac, 40 bar CO/H_2 and 80 °C for 24 h in 59% yield (66.0 mg, 0.2 mmol) as a 4 : 1 mixture of diastereoisomers.

***cis*-Diastereoisomer.**

^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 6H, 2 × C*H*$_3$); 0.89 (s, 9H, *t-Bu*); 1.05 (d, J = 4 Hz, 3H, C*H*$_3$); 1.13 (s, 3H, C*H*$_3$); 1.18 (s, 3H, C*H*$_3$); 1.74–1.81 (m, 2H, CH_2); 1.98–2.08 (m, 2H, CH_2); 2.78 (dq, J = 3, 5 Hz, 1H, α-C*H*); 3.45 (dt, J = 3, 7 Hz, 1H, R_2C*H*(OTBS)). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 0.9, 11.3, 16.4, 23.0, 24.3, 25.3, 25.8, 26.5, 27.3, 27.6, 27.7, 32.1, 51.2, 81.4, 212.7. FTIR ($CDCl_3$ film): 2977, 2932, 2872, 1712, 1383, 1111, 909, 734. HR-EIMS anal. calc. for $C_{15}H_{30}O_2Si$: 270.2015; anal. found: 270.2020.

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