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An Efficient Directed Claisen Reaction Allows for Rapid Construction of 5,6-Disubstituted 1,3-Dioxin-4-ones

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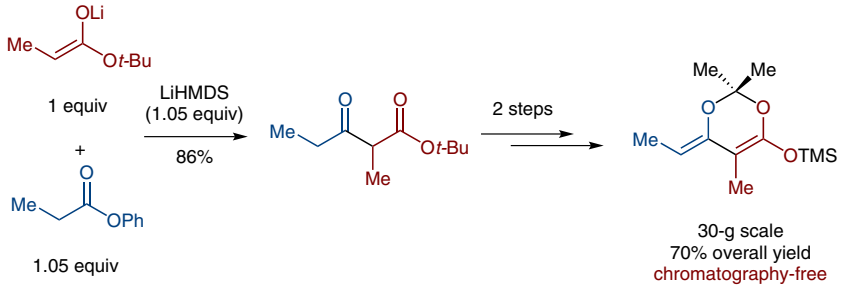

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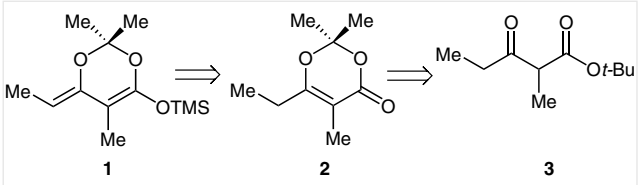
Abstract An efficient directed Claisen reaction between *tert*-butyl propionate and phenyl propionate is described. This enables a practical synthesis of 6-ethyl-2,2,5-trimethyl-4*H*-1,3-dioxin-4-one and thereby (*Z*)-[(4-ethylidene-2,2,5-trimethyl-4*H*-1,3-dioxin-6-yl)oxy]trimethylsilane, a key building block in our synthesis of macrolide antibiotics. The three-step route elaborated for the preparation of the latter substance requires no chromatography and is amenable to large-scale synthesis.

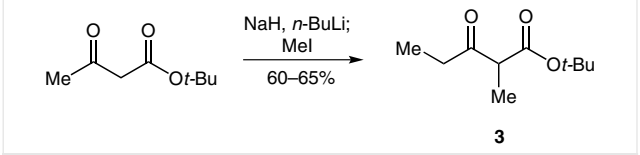
Key words directed Claisen reaction, β-keto ester synthesis, phenyl ester substrate, synthesis of substituted dioxinones, macrolide antibiotics

We have developed a practical synthetic route to macrolide antibiotics that involves the highly convergent assembly of eight simple building blocks. To enable large-scale synthesis of macrolide antibiotic candidates for potential clinical development, it is essential that each of our simple molecular building blocks be available in large quantities from readily available commodity chemicals. One essential building block is (*Z*)-[(4-ethylidene-2,2,5-trimethyl-4*H*-1,3-dioxin-6-yl)oxy]trimethylsilane (**1**). Here we detail a directed Claisen strategy that permits a practical, large-scale synthesis of this substance.

Kato and co-workers have reported a facile method for the synthesis of 2,2-dimethyl-1,3-dioxinones from β-keto *tert*-butyl esters, acetic anhydride, acetone, and sulfuric acid.[1] To implement this method to synthesize the dioxinone **2** an access to the *tert*-butyl ester **3** is required (Scheme 1). A two-step sequential γ-, then α-dimethylation of *tert*-butyl acetoacetate has been reported to produce **3** in 51% yield,[2] but a shorter and more efficient sequence was sought. We found that a single-step α,γ-dimethylation of *tert*-butyl acetoacetate (Scheme 2) was feasible and afforded the desired product **3** in 60–65% yield, but its purification was complicated by the presence of γ-monomethylated and α,α,γ-trimethylated by-products, which were difficult to separate.



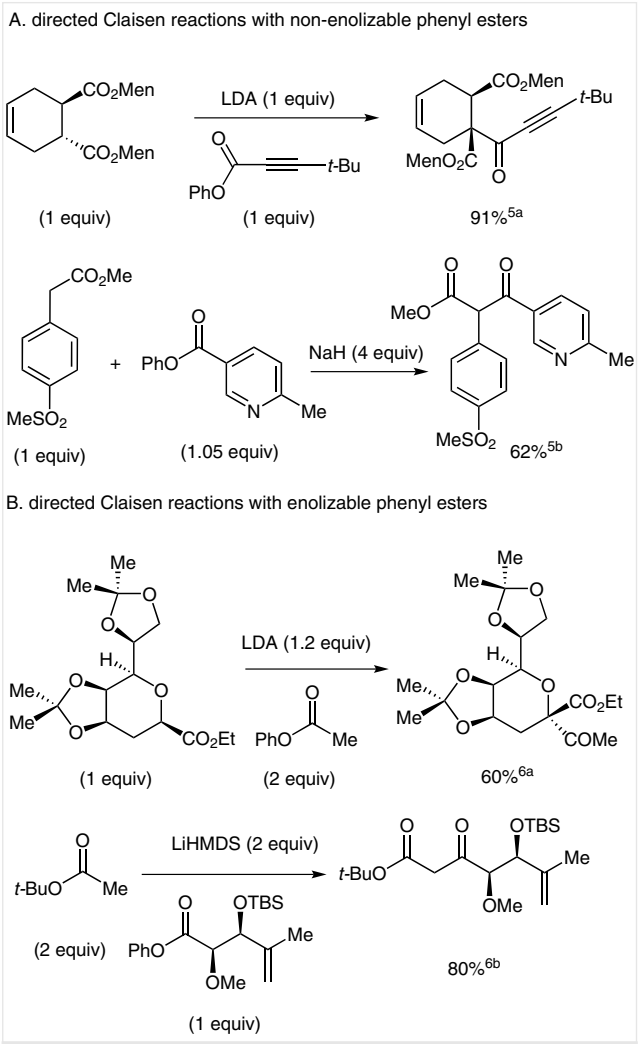
Scheme 1 Retrosynthetic route to **1**



Scheme 2 A single-step synthesis of **3**

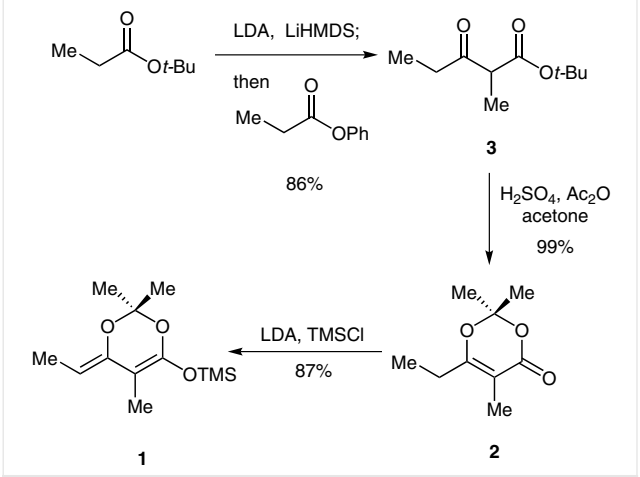
In light of previous successes in other laboratories[3] as well as ours[4] employing phenyl esters as substrates in intramolecular Claisen condensations, we envisioned that **3** might be assembled efficiently by a directed Claisen reaction between *tert*-butyl propionate and phenyl propionate. Two prior examples each of nonenolizable[5] and enolizable[6] phenyl esters as condensation partners in directed Claisen reactions are summarized graphically in Scheme 3. Whereas condensations of nonenolizable phenyl esters can be conducted with equimolar amounts of the two coupling partners (Scheme 3, A), in the examples of directed Claisen reactions with enolizable phenyl esters as electrophiles an excess of either the enolate or the phenyl ester was necessary (Scheme 3, B). In the protocol detailed herein, efficient

coupling between *tert*-butyl propionate and phenyl propionate was achieved using just a 5% excess of the latter reactant.



Scheme 3 Previous examples of directed Claisen reactions with phenyl ester electrophiles

As shown in Scheme 4 below, addition of *tert*-butyl propionate (1 equiv, 30.7 g) to a solution of LDA (1.025 equiv) in THF at –78 °C followed immediately in sequence by additions of a freshly prepared solution of lithium hexamethyldisilazide (1.0 M, 1.05 equiv) in THF and a solution of phenyl propionate in THF (5.0 M, 1.05 equiv) led to complete and clean directed condensation within one hour at –78 °C, as determined by TLC analysis. Extractive isolation (including a basic aqueous wash to remove the by-product phenol) and concentration afforded the crude Claisen product in 86% yield (37.8 g). ^{1}H NMR analysis showed that the product was free from detectable impurities; it was therefore used without further purification. Inclusion of one equivalent of lithium hexamethyldisilazide was key to achieving a high yield, and is believed to serve to deprotonate the β-keto *tert*-butyl ester product as it is formed, preventing nonproductive consumption of the *tert*-butyl ester enolate. The use of additional base in Claisen couplings has been reported previously by Ohta and co-workers[7] for condensations between the lithium enolate of *tert*-butyl acetate and methyl or ethyl alkanoates, although in these examples slow addition of an excess of the nucleophilic ester component (2 equiv) and base (2.5 equiv) was required. The use of an extra equivalent of base had also earlier been shown to be beneficial in improving the yield of certain intramolecular Claisen cyclization reactions that we investigated as part of our research on the synthesis of tetracyclines.[4c] The important role of the phenyl ester substrate in the present transformation merits brief comment. Its high reactivity as a Claisen substrate permits rapid condensation to occur even at –78 °C without enolate exchange (deprotonation of phenyl propionate by lithium *tert*-butyl propionate). In addition, the acidity of the phenol by-product permits its facile removal by base extraction. By contrast, when the condensation of lithium *tert*-butyl propionate was attempted with benzyl propionate at –78 °C no reaction was observed at that temperature, and at warmer temperatures where condensation did proceed, self-condensation of benzyl propionate was observed as well as the desired cross-coupling product **3**.



Scheme 4 Large-scale synthesis of **1** by directed Claisen reaction

Treatment of a solution of the (unpurified) product **3** in acetone (6.8 M) with acetic anhydride (3.0 equiv) and concentrated sulfuric acid (1.0 equiv) at 23 °C for five hours, as specified by Kato et al.,[1] afforded 2,2,6-trimethyl-5-ethyl-1,3-dioxin-4-one (**2**) in quantitative yield as a colorless liquid. If desired, this product can be purified by distillation, although the crude product is quite pure. Further transformation of **2** into the corresponding trimethylsilyl enol ether **1** was easily achieved by enolization at –78 °C with LDA (1.2 equiv) followed by addition of freshly distilled chloro-

trimethylsilane (1.2 equiv). Extractive isolation and distillation afforded pure (*Z*)-**1** in 87% yield. The *E*-stereoisomer is not formed, presumably as a consequence of an unfavorable $A_{1,3}$ steric repulsion that would be present between the methyl groups in that isomer. Pure (*Z*)-**1** has been found to be stable to storage in neat form at –15 °C for at least one year.

The three-step sequence described above requires no chromatography and is amenable to large-scale synthesis. We have conducted this sequence several times over to afford 30-gram batches of pure (*Z*)-**1** in an overall yield of ~70% from *tert*-butyl propionate. We believe that the protocols reported here may be of value in the preparation of other Claisen products and thereby substituted 1,3-dioxinones.

All reactions were performed in flame-dried glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Solutions were concentrated by rotary evaporation below 35 °C. Analytical TLC was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), then were stained by submersion in a 10% solution of phosphomolybdic acid (PMA) in EtOH, followed by brief heating on a hot plate.

Commercial solvents and reagents were used as received with the following exceptions. Hexamethyldisilazine (HMDS), *i*-Pr_2NH, and Me_3SiCl were distilled from CaH_2 under an atmosphere of N_2 at 760 mmHg. Et_2O, and THF were purified by passage through Al_2O_3 under argon by the method of Pangborn et al.[8] The molarity of solutions of *n*-BuLi was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[9]

^1H and ^{13}C NMR spectra were recorded on Varian INOVA 500 (500 MHz/125 MHz) or INOVA 600 (600 MHz/150 MHz) NMR spectrometer at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ = 7.26). Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ = 77.0). Data are represented as follows: chemical shift, multiplicity (standard abbreviations), coupling constant (*J*) in hertz (Hz), and integration. IR spectra were obtained using a Shimadzu 8400S FT-IR spectrophotometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), and intensity of absorption (s = strong, m = medium). High-resolution mass spectra were obtained at the Harvard University Mass Spectrometry Facility using a Bruker micrOTOF-QII mass spectrometer.

tert-Butyl 2-Methyl-3-oxopentanoate (3)

A solution of *n*-BuLi in hexanes (2.34 M, 106 mL, 248 mmol, 1.05 equiv) was added dropwise via cannula to an ice-cooled solution of hexamethyldisilazane (51.9 mL, 248 mmol, 1.05 equiv) in THF (90 mL). The resulting colorless solution was stirred at 0 °C for 30 min. The resulting solution of lithium hexamethyldisilazide was used within 1 h. In a separate flask, a solution of *n*-BuLi in hexanes (2.34 M, 103 mL, 242 mmol, 1.025 equiv) was added dropwise via cannula to a solution of *i*-Pr_2NH (34.5 mL, 242 mmol, 1.025 equiv) in THF (104 mL) at –78 °C (dry ice/acetone bath). The resulting colorless solution was stirred at –78 °C for 15 min. A solution of *tert*-butyl propionate (30.7 g, 236 mmol, 1 equiv) in THF (50 mL) was added dropwise via cannula. The resulting pale yellow solution was stirred at –78 °C for 15 min, then the freshly prepared solution of lithium hexamethyldisilazide (vide supra) was added dropwise via cannula. Immediately following completed addition, a solution of phenyl propionate (37.2 g, 248 mmol) in THF (50 mL) was added dropwise via cannula. The resulting solution was stirred at –78 °C for 1 h. Sat. aq NH_4Cl (200 mL), H_2O (400 mL), and Et_2O (400 mL) were added sequentially, and the mixture was allowed to warm to 23 °C with stirring. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 300 mL). To the combined organic layers was added 2 M aq NaOH (500 mL), and the biphasic mixture was stirred vigorously for 2 h. The layers were separated and the organic layer was washed with H_2O (500 mL) followed by brine (500 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure [rotary evaporation, 30 °C (water bath)/~40 mmHg] to provide **3** as a pale yellow oil; yield: 37.8 g (86%).

FTIR (neat): 2980 (m), 1735 (s), 1715 (s), 1369 (m), 1155 (s), 847 (m), 735 cm^{-1} (m).

^1H NMR (600 MHz, $CDCl_3$): δ = 3.42 (q, *J* = 7.3 Hz, 2 H), 2.64–2.46 (m, 1 H), 1.45 (s, 9 H), 1.29 (d, *J* = 6.6 Hz, 3 H), 1.08 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.8, 169.8, 81.6, 53.6, 34.5, 27.9, 12.7, 7.7.

HRMS (ESI): *m*/*z* calcd for $(C_{10}H_{18}O_3 + Na)^+$: 209.1148; found: 209.1148.

6-Ethyl-2,2,5-trimethyl-4*H*-1,3-dioxin-4-one (2)

Ac_2O (55.3 mL, 586 mmol, 3.00 equiv) was added dropwise via addition funnel to a solution of *tert*-butyl 2-methyl-3-oxopentanoate (**3**; 36.4 g, 195 mmol, 1 equiv) in acetone (28.7 mL, 391 mmol, 2.00 equiv) at 0 °C (ice-water bath). Concd H_2SO_4 (10.4 mL, 195 mmol, 1.00 equiv) was then added to the ice-cold solution dropwise over 15 min via addition funnel. The reaction solution was allowed to warm to 23 °C and stirred at that temperature for 5 h. The mixture was poured into a 3 L flask containing Et_2O (1 L) and sat. aq $NaHCO_3$ (1.6 L). The biphasic mixture was stirred for 2 h and the layers were separated. The organic layer was washed with sat. aq $NaHCO_3$ (2 × 1 L) followed by brine (1 L). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure [rotary evaporation, 30 °C (water bath)/~40 mmHg] to provide **2** as a colorless oil; yield: 32.8 g (99%). The product, if desired, can be distilled under reduced pressure (70 °C/0.5 mmHg, ~75% yield).

FTIR (neat): 2991 (m), 1720 (s), 1643 (s), 1388 (s), 1377 (s), 1361 (s), 1267 (s), 1205 (s), 1150 (s), 1080 (s), 981 (s), 862 (m), 767 cm^{-1} (s).

^1H NMR (600 MHz, $CDCl_3$): δ = 2.30 (q, *J* = 7.6 Hz, 2 H), 1.82 (s, 3 H), 1.65 (s, 6 H), 1.12 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7, 162.8, 104.5, 99.3, 24.9, 24.2, 10.2, 9.7.

HRMS (ESI): *m*/*z* calcd for $(C_9H_{14}O_3 + H)^+$: 171.1016; found: 171.1023.

(*Z*)-[(4-Ethylidene-2,2,5-trimethyl-4*H*-1,3-dioxin-6-yl)oxy]trimethylsilane (1)

A solution of *n*-BuLi in hexanes (2.32 M, 76 mL, 176 mmol, 1.20 equiv) was added dropwise via cannula to a solution of *i*-Pr_2NH (25.1 mL, 176 mmol, 1.20 equiv) in THF (210 mL) at –78 °C (dry ice/acetone bath). The reaction flask was transferred to an ice bath and stirring was continued for 15 min. The reaction flask was cooled to –78 °C,

and a solution of 6-ethyl-2,2,5-trimethyl-4*H*-1,3-dioxin-4-one (**2**; 25.0 g, 147 mmol, 1 equiv) in THF (50 mL) was added dropwise via cannula; the transfer was quantitated with additional THF (6 mL). The reaction mixture was stirred for 1 h at –78 °C, then Me_3SiCl (22.5 mL, 176 mmol, 1.20 equiv) was added dropwise via syringe. After stirring for 3 h at –78 °C, the cooling bath was removed and the reaction mixture was allowed to warm to 23 °C, whereupon it was then concentrated under reduced pressure [rotary evaporation, 30 °C (water bath)/~40 mmHg]. The residue was diluted with anhydrous pentane (100 mL) and the resulting suspension was filtered through a sintered glass funnel (medium porosity, 10–15 µm pore size). The filtrate was concentrated to afford a yellow residue, which was purified by vacuum distillation (63–67 °C/0.2 mmHg) to afford **1** as a colorless oil; yield: 31.0 g (87%).

FTIR (neat): 2997 (m), 1678 (s), 1253 (s), 1170 (m), 910 (s), 885 (s), 846 (s), 730 cm^{-1} (s).

^1H NMR (500 MHz, $CDCl_3$): δ = 4.40 (q, *J* = 6.9 Hz, 1 H), 1.66 (d, *J* = 6.9 Hz, 3 H), 1.63 (s, 3 H), 1.52 (s, 6 H), 0.24 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.9, 147.2, 101.0, 95.0, 82.1, 24.7, 9.9, 9.1, 0.5.

HRMS (ESI): *m*/*z* calcd for $(C_{12}H_{22}O_3Si + H)^+$: 243.1411; found: 243.1416.

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