Formation of β-Substituted γ-Keto Esters via Zinc Carbenoid Mediated Chain Extension

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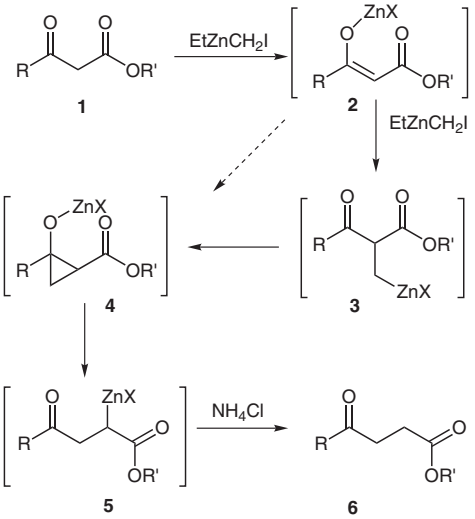
Dedicated to Professor Paul Wender in honor of his 60th birthday

Abstract: The conversion of β-keto esters into β-methylated γ-keto esters can be achieved through treatment with zinc carbenoids derived from 1,1-diiodoethane. The incorporation of a β-phenyl substituent is also possible through treatment with diiodotoluene.

Key Words: carbenoids, diiodoethane, esters, chain extension, zinc

Chain-extension reactions based upon the intermediacy of donor–acceptor cyclopropanes have been used to prepare a variety of γ-dicarbonyl species.[1] In this vein, a one-step zinc carbenoid mediated chain-extension reaction has been developed in our laboratories in which β-keto esters **1** can be transformed into γ-keto carbonyls through application of the Furukawa modification of the Simmons–Smith reagent.[2] A proposed mechanism (Scheme 1) for the chain extension involves enolate **2** formation of the β-keto ester followed by formation of the donor–acceptor cyclopropane **4**. It is unclear whether the formation of the putative cyclopropane is concerted or involves a stepwise alkylation–cyclization process. Fragmentation of the donor–acceptor cyclopropane provides an organometallic intermediate **5**, which can be quenched with a proton to provide the chain extended compound **6**. The proposed mechanism is consistent with the observation that the carbenoid carbon is inserted adjacent to the ketone.

Tandem reaction sequences have been developed in which the reaction's organometallic intermediate is functionalized with a variety of electrophiles. Variations have allowed the incorporation of hydroxyalkyl substituents,[3] methyl groups,[4] and iodomethyl groups at the α-position.[5] Other variations on the reaction allow the direct incorporation of iodine, which can be eliminated to generate an α,β-unsaturated-γ-keto carbonyl.[6] The latter variation provides the opportunity for incorporation of even greater diversity at the α-position through conjugate addition strategies.[7] None of these strategies, however, facilitate the incorporation of substituents at the β-position. The ability to incorporate substituents at the β-carbon would greatly expand the utility of the zinc carbenoid mediated chain-extension reaction.



Scheme 1 Mechanism for zinc carbenoid mediated chain extension

The β-carbon in the product is derived from the carbenoid, hence from diiodomethane; therefore, incorporation of substituents at the β-carbon will require the use of homologous 1,1-diiodoalkanes. While 1,1-diiodoalkanes have been used in conjunction with diethylzinc for the formation of substituted cyclopropanes,[8] their use for the formation of donor–acceptor cyclopropanes has not been reported. Herein, we describe the chain extension of β-keto esters and amides with 1,1-diiodoethane **7** and α,α-diiodotoluene **8**.

1,1-Diodoalkanes can be generated through a number of methods.[9] The formation of 1,1-diodoethane (**7**) was accomplished by treatment of the corresponding dichloride with ethyl iodide in the presence of aluminum chloride.[10] α,α-Diiodotoluene (**8**) was prepared through treatment of benzaldehyde with trimethylsilyl iodide (TMSI).[11]

We were pleased to observe that the chain extension of various β-keto esters **9** with the carbenoid derived from 1,1-diiodoethane proceeded with good yields (Table 1). We found that the reaction proceeded efficiently when the zinc enolate was formed by treatment of the β-keto ester with diethylzinc prior to addition of the diiodoalkane. The alternate procedure, in which the carbenoid was generated prior to addition of the β-keto ester, frequently resulted in incomplete conversion of the starting material. If incomplete conversion of the starting material to product was

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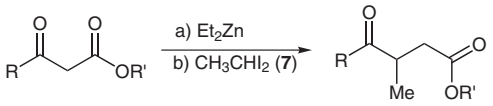
Table 1 Chain Extension of β-Keto Esters with the Carbenoid Derived from **7**



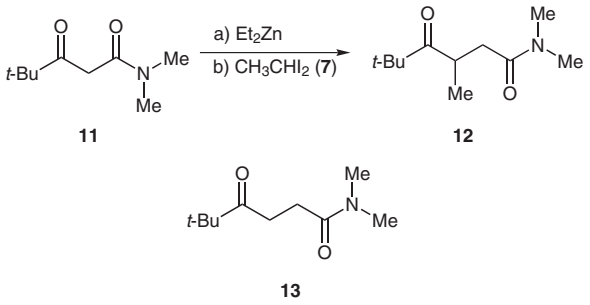
9a–f **10a–f**

Entry	R	R′	Product	Yield (%)
1	Me	Me	**10a**	76
2	Me	*t*-Bu	**10b**	88
3	*t*-Bu	Me	**10c**	82
4	Me	$CH_2CH{=}CH_2$	**10d**	74
5	Ph	Et	**10e**	84
6	Me	Bn	**10f**	80

observed by TLC, as was the case with the formation of **10d**, the addition of a second portion of carbenoid was generally sufficient for complete conversion.

The use of β-keto tertiary amides as starting materials was also investigated. While no difference in reactivity between β-keto esters and β-keto tertiary amides is observed when chain-extension reactions are performed with diiodomethane, the use of 1,1-diiodoethane revealed dramatic differences. *N*,*N*-Dimethylpivaloylacetamide (**11**)[12] was chosen as the initial substrate due to its analogy with methyl pivaloylacetate (**9c**), which has been shown to undergo chain extension with both diiodomethane and 1,1-diodoethane in high yield. Identical reaction conditions, involving enolate formation with the addition of diethylzinc prior to generation of the carbenoid, were applied to the amide substrate (Scheme 2). Compound **12**, the anticipated β-methylated product, was observed in the crude reaction mixture; however, analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed a 2:1 ratio of starting material **11** to **12**. This was an unexpected result, since methyl pivaloylacetate (**9c**) treated with the carbenoid derived from 1,1-diiodoethane was completely consumed under the identical reaction conditions. No evidence for the formation of any other product resulting from alkylation of the enolate was observed, even though α-alkylation products had been observed in earlier studies of the zinc-mediated chain extension when chain extension was incomplete. Increasing the time allowed for enolate formation from 10 to 20 minutes or increasing the reaction time with carbenoid from 30 minutes to 2 hours did not change this ratio.

The consistency in the ratio of starting material to desired product, in addition to the lack of other products derived from the starting material, suggested that the alkylation step of the proposed mechanism was not taking place. Although all starting materials were rigorously dried, the potential for quenching enolate formation through a proton source was probed by increasing the equivalencies of



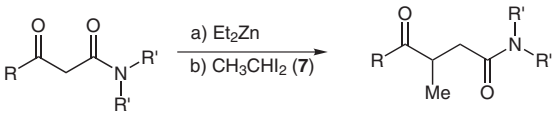
Scheme 2 Chain extension with 1,1-diiodoethane

Et_2Zn; however, no improvement in the reaction conversion was observed. Changing the ratio of Et_2Zn/CH_3CHI_2 to 1.5:1 did not result in increased conversion.[13] However, after the β-keto amide was treated with excess diethylzinc and 1,1-diiodoethane (**7**) for 90 minutes, the addition of diiodomethane resulted in immediate consumption of β-keto amide **11** and formation of the unsubstituted chain extended product **13**.[2b] This confirmed that the enolate was still present, but that its reaction with the carbenoid derived from **7** was not taking place.

More β-keto amides **14a**,**b** were exposed to the chain-extension reaction conditions using diiodoethane. Increased steric bulk at the ketone terminus of the β-keto amide, in combination with the increased size of the carbenoid derived from 1,1-diiodoethane, appears to hinder the formation of the initial carbon–carbon bond. However, less hindered substituents were well tolerated, which resulted in complete conversion to the chain extended products in synthetically useful yields (Table 2).

Decomposition of ethyl(iodomethyl)zinc, the carbenoid derived from diiodomethane, has been reported,[14] although the chain-extension reaction involving ethyl(iodomethyl)zinc is apparently fast enough to negate the effects of decomposition. The chain-extension reaction involving carbenoid **7** appears to be slower, perhaps allowing a decomposition pathway to compete. Competitive decomposition could explain the necessity of adding a second dose of carbenoid in some instances. 2-Iodobutane was observed in all of the carbenoid reactions involv-

Table 2 Chain Extension of β-Keto Amides with the Carbenoid Derived from **7**



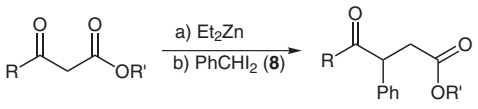
14a,**b** **15a**,**b**

Entry	R	R′	Product	Yield (%)
1	Me	Me	**15a**	67
2	Me	$-(CH_2)_4-$	**15b**	74
3	*i*-Pr	Me	**15c**	incomplete conversion

ing 1,1-diiodoethane.[15] Although the carbenoid from **7** is typically prepared through the use of large excesses of both diethylzinc and 1,1-diiodoethane, the appearance of 2-iodobutane as a major byproduct of carbenoid preparation provides further understanding into the need to add a second dose of carbenoid.

Treatment of β-keto esters **9a** and **9b** with the carbenoid derived from α,α-diiodotoluene **8** provided γ-keto esters **16a** and **16b** with the incorporation of an aryl group at the β-position (Table 3). The reactions were lower yielding than the chain extension with the 1,1-diiodoethane **7**, but the incorporation of the aryl group at the β-position was still efficient and completely regioselective. Efforts to chain-extend *N*,*N*-dimethylacetoacetamide (**15a**) with **8** resulted in the recovery of starting material.

Table 3 Chain Extension of β-Keto Esters with the Carbenoid Derived from **8**



Entry	R	R′	Product	Yield (%)
1	Me	Me	**16a**	74
2	Me	*t*-Bu	**16b**	44

In summary, we have been able to demonstrate that zinc carbenoids derived from 1,1-diiodoethane and α,α-diiodotoluene can be used to chain-extend β-keto esters and β-keto amides. This variation on the zinc carbenoid mediated chain-extension reaction provides the opportunity to incorporate substituents at the β-position, where conjugate addition and enolate strategies for substituent incorporation are not options. Efforts to further diversify the carbenoids used in the chain-extension reaction, to control the stereochemistry at the β-position, and to perform tandem reactions involving the organometallic intermediate are under investigation.

Oven-dried glassware and Teflon-coated magnetic stir bars were used for all reactions. Solvents were dried by passing the solvent through a column of alumina. The diethylzinc used in chain-extension reactions was commercially available as a 1.0 M solution in hexanes. Column chromatography was performed using Sorbent Technologies flash silica gel (32–63 μm). The reported R_f values refer to the use of the column chromatography solvent systems with F254 glass TLC plates from EM Science. Anisaldehyde stain and UV was employed for visualization in TLC analysis.

NMR spectroscopy was performed on Varian Mercury operating at 399.751 MHz for ^{1}H nuclei and 100.528 MHz for ^{13}C nuclei and Varian Inova operating at 499.766 MHz and 125.679 MHz for ^{1}H nuclei and ^{13}C nuclei, respectively. All NMR experiments were carried out in $CDCl_3$ solvent. All chemical shifts are reported in ppm relative to tetramethylsilane.

Rotary evaporation was performed at reduced pressures between 12 and 60 mmHg. Temperatures varied between r.t. and 30 °C. The N_2 gas inlets used in experiments consisted of a needle attached to a N_2 line. Filtration of drying agents from organic extracts was performed at atmospheric pressure with filter paper.

Methyl 3-Methyl-4-oxopentanoate (10a)

A 25-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of N_2 through a needle was charged with CH_2Cl_2 (8 mL) and diethylzinc (1.0 M in hexanes, 2.5 mL, 2.5 mmol). The mixture was cooled to 0 °C and a solution of methyl acetoacetate (58 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) was added. After stirring for 10 min, 1,1-diiodoethane (0.25 mL, 2.5 mmol) was added dropwise by syringe. The mixture was stirred for 1 h at r.t., quenched by cautious addition of sat. aq NH_4Cl (5 mL) and extracted with Et_2O (3 × 8 mL). The combined organic extracts were washed with brine (5 mL) and dried (Na_2SO_4). The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica gel (R_f = 0.30, hexane–EtOAc, 7:1) to give 55 mg (76%) of the known compound **10a**[16] as a colorless liquid.

IR (neat): 2955, 1737, 1716, 1437 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.64 (s, 3 H), 2.99 (m, 1 H), 2.74 (dd, *J* = 8.6, 16.7 Hz, 1 H), 2.28 (dd, *J* = 5.5, 16.8 Hz, 1 H), 2.20 (s, 3 H), 1.14 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.7, 172.7, 51.7, 42.7, 36.6, 28.4, 16.5.

HRMS (EI): *m*/*z* calcd for $C_7H_{12}O_3$: 144.0786; found: 144.0791.

***tert*-Butyl 3-Methyl-4-oxopentanoate (10b)**

A 25-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of N_2 through a needle was charged with CH_2Cl_2 (8 mL) and diethylzinc (1.0 M in hexanes, 2.5 mL, 2.5 mmol). The mixture was cooled to 0 °C and a solution of *tert*-butyl acetoacetate (79 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) was added. After stirring for 10 min, 1,1-diiodoethane (0.25 mL, 2.5 mmol) was added dropwise by syringe. The mixture was stirred for 1 h at r.t., quenched by cautious addition of sat. aq NH_4Cl (5 mL) and extracted with Et_2O (3 × 8 mL). The combined organic extracts were washed with brine (5 mL) and dried (Na_2SO_4). The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica gel (R_f = 0.50, hexane–EtOAc, 7:1) to afford 82 mg (88%) of the targeted compound **10b** as a colorless liquid.

IR (neat): 2977–2934, 1727, 1717, 1367 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.95 (m, 1 H), 2.66 (dd, *J* = 8.6, 16.5 Hz, 1 H), 2.23 (dd, *J* = 5.5, 16.5 Hz, 1 H), 2.21 (s, 3 H), 1.43 (s, 9 H), 1.13 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.8, 171.4, 80.6, 42.9, 38.2, 28.3, 28.0, 16.3.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{18}O_3$: 186.1256; found: 186.1252.

Methyl 3,5,5-Trimethyl-4-oxohexanoate (10c)

A 25-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of N_2 through a needle was charged with CH_2Cl_2 (8 mL) and diethylzinc (1.0 M in hexanes, 2.5 mL, 2.5 mmol). The mixture was cooled to 0 °C and a solution of methyl pivaloylacetate (79 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) was added to the solution. After stirring for 10 min, 1,1-diiodoethane (0.25 mL, 2.5 mmol) was added dropwise by syringe. The mixture was stirred for 1 h at r.t., quenched by cautious addition of sat. aq NH_4Cl (5 mL) and extracted with Et_2O (3 × 8 mL). The combined organic extracts were washed with brine (5 mL) and dried (Na_2SO_4). The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica gel (R_f = 0.64, hexane–EtOAc, 7:1) to afford 76 mg (82%) of the known compound **10c**[17] as a colorless liquid.

IR (neat): 2972–2956, 1740, 1703, 1480, 1437 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.61 (s, 3 H), 3.43 (m, 1 H), 2.66 (dd, *J* = 8.0, 16.4 Hz, 1 H), 2.28 (dd, *J* = 6.3, 16.4 Hz, 1 H), 1.16 (s, 9 H), 1.05 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 218.1, 172.5, 51.5, 44.5, 38.1, 36.2, 26.5, 18.3.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{18}O_3$: 186.1256; found: 186.1253.

Allyl 3-Methyl-4-oxopentanoate (10d)

A 25-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of N_2 through a needle was charged with CH_2Cl_2 (8 mL) and diethylzinc (1.0 M in hexanes, 1.5 mL, 1.5 mmol). The mixture was cooled to 0 °C and a solution of allyl acetoacetate (73 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) was added. After stirring for 10 min, 1,1-diiodoethane (0.15 mL, 1.5 mmol) was added dropwise by syringe. The mixture was stirred for 0.5 h at r.t. Diethylzinc (1.0 M in hexanes, 1.5 mL, 1.5 mmol) was added at r.t. to the mixture and after 10 min, 1,1-diiodoethane (0.15 mL, 1.5 mmol) was added dropwise by syringe. The mixture was stirred for 0.5 h at r.t., quenched by cautious addition of sat. aq NH_4Cl (5 mL) and extracted with Et_2O (3 × 8 mL). The combined organic extracts were washed with brine (5 mL) and dried (Na_2SO_4). The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (R_f = 0.37, hexane–EtOAc, 7:1) to give 63 mg (74%) of compound **10d** as a colorless liquid.

IR (neat): 3021–2936, 1733, 1716, 1460 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.89 (m, 1 H), 5.30 (dd, *J* = 1.5, 17.2 Hz, 1 H), 5.22 (dd, *J* = 1.3, 10.4 Hz, 1 H), 4.56 (dd, *J* = 1.4, 1.4 Hz, 1 H), 4.55 (dd, *J* = 1.4, 1.4 Hz, 1 H), 3.01 (m, 1 H), 2.79 (dd, *J* = 8.7, 16.8 Hz, 1 H), 2.32 (dd, *J* = 5.4, 16.8 Hz, 1 H), 2.21 (s, 3 H), 1.15 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.6, 171.9, 132.0, 118.3, 65.2, 42.7, 36.8, 28.4, 16.5.

HRMS (EI): *m*/*z* calcd for $C_9H_{14}O_3$: 170.0943; found: 170.0946.

Ethyl 3-Methyl-4-oxo-4-phenylbutanoate (10e)

A 25-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of N_2 through a needle was charged with CH_2Cl_2 (8 mL) and diethylzinc (1.0 M in hexanes, 2.5 mL, 2.5 mmol). The mixture was cooled to 0 °C and a solution of ethyl benzoylacetate (96 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) was added. After stirring for 10 min, 1,1-diiodoethane (0.25 mL, 2.5 mmol) was added dropwise by syringe. The mixture was stirred for 1 h at r.t., quenched by cautious addition of sat. aq NH_4Cl (5 mL) and extracted with Et_2O (3 × 8 mL). The combined organic extracts were washed with brine (5 mL) and dried (Na_2SO_4). The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica gel (R_f = 0.52, hexane–EtOAc, 7:1) to afford 92 mg (84%) of the known compound **10e**[18] as a colorless liquid.

IR (neat): 2979, 1733, 1683, 1448, 1377 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.98–7.96 (m, 2 H), 7.54 (m, 1 H), 7.47–7.44 (m, 2 H), 4.08 (q, *J* = 7.1 Hz, 2 H), 3.94 (m, 1 H), 2.94 (dd, *J* = 8.5, 16.7 Hz, 1 H), 2.44 (dd, *J* = 5.7, 16.7 Hz, 1 H), 1.20 (t, *J* = 7.3 Hz, 3 H), 1.18 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.7, 172.2, 135.9, 133.0, 128.6, 128.3, 60.5, 37.5, 37.1, 17.7, 14.0.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{16}O_3$: 220.1099; found: 220.1101.

Benzyl 3-Methyl-4-oxopentanoate (10f)

A 25-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of N_2 through a needle was charged with CH_2Cl_2 (8 mL) and diethylzinc (1.0 M in hexanes, 2.5 mL, 2.5 mmol). The mixture was cooled to 0 °C and a solution of benzyl acetoacetate (96 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) was added. After stirring for 10 min, 1,1-diiodoethane (0.25 mL, 2.5 mmol) was added dropwise by syringe. The mixture was stirred for 1 h at r.t., quenched by cautious addition of sat. aq NH_4Cl (5 mL) and extracted with Et_2O (3 × 8 mL). The combined organic extracts were washed with brine (5 mL), and dried (Na_2SO_4). The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica gel (R_f = 0.30, hexane–EtOAc, 7:1) to give 88 mg (80%) of the targeted compound **10f** as a colorless liquid.

IR (neat): 2969–2934, 1734, 1715, 1456 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.30 (m, 5 H), 5.11–5.08 (d, *J* = 4.7 Hz, 2 H), 3.03 (m, 1 H), 2.82 (dd, *J* = 8.7, 16.8 Hz, 1 H), 2.34 (dd, *J* = 5.4, 16.8 Hz, 1 H), 2.20 (s, 3 H), 1.15 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.6, 172.1, 135.8, 128.5, 128.2, 128.1, 66.4, 42.7, 36.8, 28.3, 16.5.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{16}O_3$: 220.1099; found: 220.1097.

***N*,*N*,3-Trimethyl-4-oxopentanamide (15a)**

Into a 25-mL round-bottomed flask equipped with a magnetic stir bar, septum, and N_2 gas inlet were added anhyd CH_2Cl_2 (5 mL). The flask was purged with N_2 and cooled to 0 °C in an ice bath. Diethylzinc (1 M in hexanes, 2.5 mL, 2.5 mmol) was added to the flask while stirring under N_2. *N*,*N*-Dimethylacetoacetamide[2b] (65 mg, 0.5 mmol) in anhyd CH_2Cl_2 (5 mL), containing molecular sieves, was added dropwise by syringe at 0 °C over 2 min and the solution was allowed to stir for 10 min. 1,1-Diiodoethane (0.25 mL, 2.5 mmol) was added dropwise to the flask at 0 °C. The formation of a white precipitate was observed after 5–10 min of stirring. After stirring at 0 °C for 2 h, the reaction was quenched with sat. aq NH_4Cl, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated on a rotary evaporator. Column chromatography (R_f = 0.15, 1:1, hexane–EtOAc) afforded **15a** as a clear yellow oil (53 mg, 67%).

^1H NMR (500 MHz, $CDCl_3$): δ = 3.14 (m, 1 H), 3.02 (s, 3 H), 2.91 (s, 3 H), 2.83 (dd, *J* = 9.5, 16 Hz, 1 H), 1.95–2.28 (m, 4 H), 1.13 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 212.2, 171.4, 50.2, 42.6, 36.9, 35.1, 29.0, 16.8.

HRMS (EI): *m*/*z* calcd for $C_8H_{15}NO_2$: 157.1103; found: 157.1100.

1-(1,4-Dioxo-3-methylpentanyl)pyrrolidine (15b)

Into a 50-mL round-bottomed flask equipped with a magnetic stir bar, septum, and N_2 gas inlet were added anhyd CH_2Cl_2 (5 mL). The flask was purged with N_2 and cooled to 0 °C in an ice bath. Diethylzinc (1 M in hexanes, 2.5 mL, 2.5 mmol) was added to the flask while stirring under N_2. 1-(Acetoacetato)pyrrolidine[2b] (74 mg, 0.5 mmol) in anhyd CH_2Cl_2 (5 mL), containing molecular sieves, was added dropwise by syringe at 0 °C over 2 min and the solution was allowed to stir for 10 min. 1,1-Diiodoethane (0.25 mL, 2.5 mmol) was added dropwise to the flask at 0 °C. The formation of a white precipitate was observed after stirring for 5–10 min. After stirring at 0 °C for 2 h, the reaction was quenched with sat. aq NH_4Cl, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated on a rotary evaporator. Column chromatography (R_f = 0.19, EtOAc–hexane, 20:1) was performed to afford **15b** as a clear yellow oil (68 mg, 74%).

^1H NMR (400 MHz, $CDCl_3$): δ = 3.34–3.52 (m, 4 H), 3.17 (m, 1 H), 2.76 (dd, *J* = 9.2, 16 Hz, 1 H), 2.26 (s, 3 H), 2.21 (dd, *J* = 4.5, 16 Hz, 1 H), 1.90–2.00 (m, 2 H), 1.79–1.90 (m, 2 H), 1.14 (d, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.5, 170.0, 46.7, 45.7, 42.5, 38.1, 29.1, 26.2, 24.6, 16.9.

HRMS (EI): *m/z* calcd for $C_{10}H_{17}NO_2$: 183.1259; found: 183.1263.

Methyl 4-Oxo-3-phenylpentanoate (16a)

A 25-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of N_2 through a needle was charged with CH_2Cl_2 (8 mL) and diethylzinc (1.0 M in hexane, 2.5 mL, 2.5 mmol). The mixture was cooled to 0 °C and a solution of methyl acetoacetate (58 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) was added. After stirring for 10 min, 1,1-diiodotoluene (0.86 g, 2.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise by syringe. The mixture was stirred for 1 h at r.t., quenched by cautious addition of sat. aq NH_4Cl (5 mL) and extracted with Et_2O (3 × 8 mL). The combined organic extracts were washed with brine (5 mL) and dried (Na_2SO_4). The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (R_f = 0.40, hexane–EtOAc, 7:1) to give 76 mg (74%) of known compound **16a**[19] as a colorless liquid.

IR (neat): 3028, 2953–2922, 1754, 1736, 1716, 1453, 1437 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.20 (m, 5 H), 4.19 (dd, *J* = 5.0, 9.8 Hz, 1 H), 3.65 (s, 3 H), 3.22 (dd, *J* = 9.9, 17.0 Hz, 1 H), 2.53 (dd, *J* = 5.0, 17.0 Hz, 1 H), 2.12 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8, 172.5, 137.3, 129.2, 128.2, 127.7, 54.8, 51.8, 36.7, 28.8.

HRMS (EI): *m/z* calcd for $C_{12}H_{14}O_3$: 206.0943; found: 206.0943.

***tert*-Butyl 4-Oxo-3-phenylpentanoate (16b)**

A 25-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of N_2 through a needle was charged with CH_2Cl_2 (8 mL) and diethylzinc (1.0 M in hexanes, 2.0 mL, 2.0 mmol). The mixture was cooled to 0 °C and a solution of *tert*-butyl acetoacetate (63 mg, 0.4 mmol) in CH_2Cl_2 (1 mL) was added to the solution. After stirring for 10 min, 1,1-diiodotoluene (0.69 g, 2.0 mmol) in CH_2Cl_2 (2 mL) was added dropwise by syringe. The mixture was stirred for 1 h at r.t., quenched by cautious addition of sat. aq NH_4Cl (5 mL) and extracted with Et_2O (3 × 8 mL). The combined organic extracts were washed with brine (5 mL) and dried (Na_2SO_4). The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica gel (R_f = 0.64, hexane–EtOAc, 7:1) to afford 44 mg (44%) of compound **16b** as a colorless liquid.

IR (neat): 2978–2930, 1719, 1367, 1355 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 5 H), 4.12 (dd, *J* = 5.3, 9.6 Hz, 1 H), 3.11 (dd, *J* = 9.8, 16.7 Hz, 1 H), 2.46 (dd, *J* = 5.3, 16.7 Hz, 1 H), 2.11 (s, 3 H), 1.39 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.9, 171.3, 137.5, 129.0, 128.3, 127.6, 80.7, 55.0, 38.2, 28.9, 28.0.

HRMS (EI): *m/z* calcd for $C_{15}H_{20}O_3$: 248.1412; found: 248.1410.

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