

Stereoselective Preparation of Functionalized Unsaturated Lactones and Esters via Functionalized Magnesium Carbenoids

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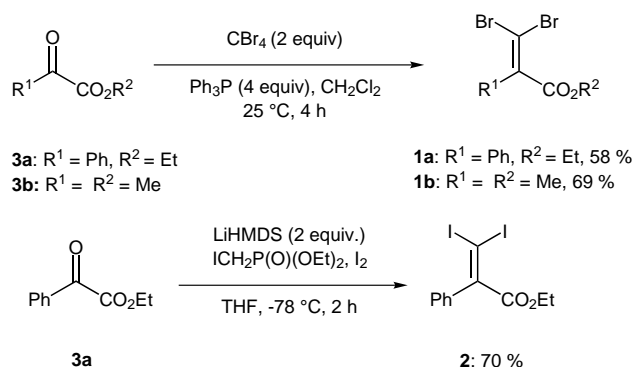
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Dedicated to Professor Wolfgang Steglich on the occasion of his 70th birthday.

Abstract: The reaction of β,β -dibromo or diiodo unsaturated esters with *i*-PrMgCl (1 equivalent) in diethyl ether allows the generation of functionalized alkenylmagnesium carbenoids which react with retention of configuration with various electrophiles providing polyfunctionalized unsaturated esters and lactones. By using two equivalents of *i*-PrMgCl, a 1,2-migration with retention of configuration occurs in diethyl ether allowing a new synthesis of tetrasubstituted esters and lactones.

Key words: functionalized magnesium carbenoids, iodine–magnesium exchange, cross-coupling, lactone synthesis, palladium catalysis

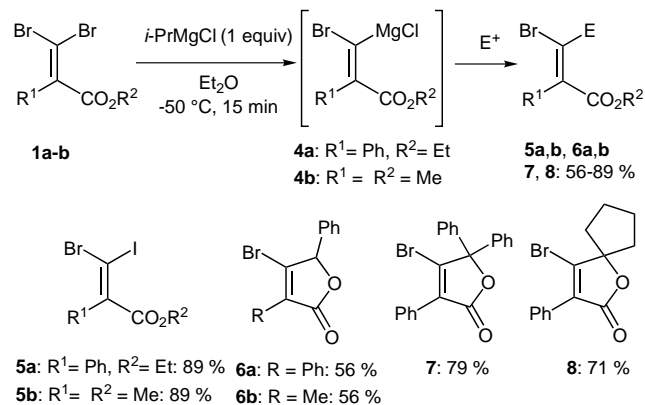
Functionalized carbenoids are potentially important intermediates for organic synthesis.¹ In continuation of our work on functionalized magnesium carbenoids² using an iodine- or bromine–magnesium exchange reaction,³ we wish to report a new stereoselective synthesis of unsaturated lactones and esters starting from dibromo esters **1a,b** and the diiodo ester **2** (Scheme 1). Thus, the reaction of ethyl phenylglyoxylate (**3a**) or methyl pyruvate (**3b**) with carbon tetrabromide and triphenylphosphine in CH₂Cl₂ (12 h, 25 °C) furnished the corresponding dibromo esters **1a** and **1b** in 58 and 69% yields, respectively.⁴ The diiodo ester **2** was also prepared from ethyl phenylglyoxylate (**3a**) using a method developed by Duhamel.⁵ Thus, the treatment of **3a** with an in situ generated lithiated diiodophosphate at –78 °C furnished the expected product **2** in 70% yield (Scheme 1).



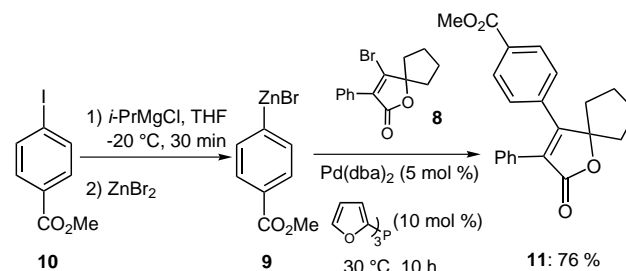
Scheme 1 Preparation of dibromo esters **1a,b** and diiodo ester **2**

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The reaction of **1a,b** with *i*-PrMgCl in diethyl ether at –50 °C for 15 minutes provided the expected magnesium carbenoids **4a,b** which can be quenched by several electrophiles like iodine, benzaldehyde, benzophenone or cyclopentanone providing the corresponding unsaturated esters **5a,b** (89% yield) or in the case of the reaction with carbonyl compounds to the unsaturated bromolactones **6a,b, 7** and **8** in 56–79% yields (Scheme 2). Interestingly, the bromolactone **8** can be further functionalized using a Negishi reaction.⁶ Thus, the reaction of **8** with the functionalized arylzinc bromide **9** prepared from methyl 4-iodobenzoate (**10**) via an iodine–magnesium exchange and a transmetalation with zinc bromide furnished, in the presence of catalytic amounts of palladium(0) bis(dibenzylideneacetone) (5 mol%)⁷ and tris(*o*-furyl)phosphine⁸ (10 mol%) at 30 °C after a reaction time of 10 hours, the desired cross-coupling product **11** in 76% yield (Scheme 3).

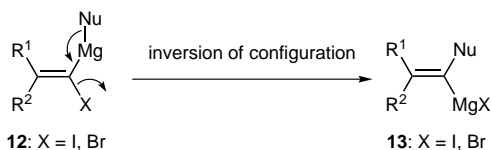


Scheme 2 Generation and reaction of magnesium carbenoids **4a,b**



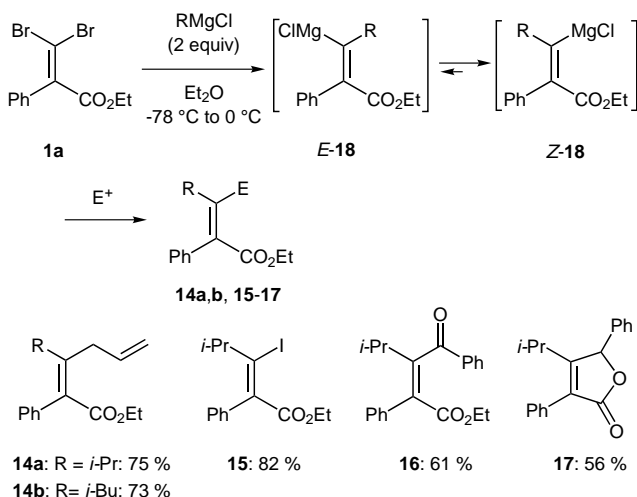
Scheme 3 Negishi cross-coupling reaction leading to the unsaturated lactone **11**

We have also examined the electrophilic reactivity of magnesium carbenoids. It is well known in the literature that a 1,2-migration occurs when carbenoid species of type **12** bear a nucleophilic substituent (Nu), which leads to products of type **13** with inversion of configuration at the carbenoid center (Scheme 4).⁹



Scheme 4 1,2-Migration of magnesium carbenoids

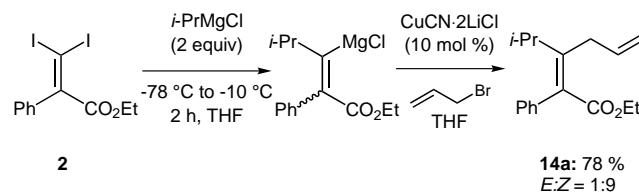
We wish to report herein the related 1,2-migration reactions proceeding formally with retention of configuration. Thus, the reaction of the dibromo ester **1a** with two equivalents of an alkylmagnesium reagent like *i*-PrMgCl or *i*-BuMgCl in diethyl ether provided after reaction with an electrophile the products **14a,b**, **15–17** in which formally the 1,2-migration has occurred with retention of configuration. The yields of the products are good (56–73%) and the stereoselectivity of the resulting open-chain unsaturated esters is excellent. For the allylated product **14a,b**, the *E/Z* ratio is >1:99 (Scheme 5).



Scheme 5 1,2-Migration of magnesium carbenoid with formal retention of configuration

The retention of configuration of the 1,2-migration is best explained by a 1,2-migration occurring with an inversion followed by an isomerization driven by a chelation stabilization. Thus, the bromine–magnesium exchange of **1a** occurs like as shown in Scheme 2 leading to the corresponding magnesium carbenoid **4a** which transfers an alkyl group (*i*-Pr or *i*-Bu) providing the *E*-magnesium reagent, (*E*)-**18**. Under the reaction conditions (−78 to 0 °C), the *E*-alkenylmagnesium compound, (*E*)-**18** isomerizes to the more stable *Z*-alkenylmagnesium species (*Z*)-**18**, which is stabilized by chelation (of the mag-

nesium atom with the carbonyl group of the ester function). Interestingly, by performing the reaction in THF which is a stronger donor solvent compared to diethyl ether, a mixture of diastereomers (*E/Z* = 1:9) was obtained after an allylation reaction performed with allyl bromide (1.1 equiv) in the presence of catalytic amounts of CuCN·2LiCl¹⁰ (Scheme 6).



Scheme 6 Copper-catalyzed allylation in THF

In summary, we have shown that the iodine- or bromine–magnesium exchange reaction on β-dibromo or β-diiodo ester of type **1** and **2** allows a stereoselective preparation of functionalized unsaturated esters. In the presence of two equivalents of an alkylmagnesium reagent, a 1,2-migration reaction occurs with an unusual retention of configuration, which allows the elaboration of stereoselectively functionalized α,β-unsaturated ester and lactones. In THF, less selective reactions are observed due to a competitive complexation of THF.

Melting points were measured on a Büchi B 540 apparatus and are uncorrected. NMR spectra were recorded in CDCl₃ at 300 MHz for ¹H NMR and 75 MHz for ¹³C NMR (Varian XL 300). Chemical shifts are reported in ppm relative to TMS. IR spectra were recorded on a Perkin-Elmer FT-IR Spectrum 1000 spectrophotometer. Low-resolution mass spectra were recorded using a GC/MS-combination of the type HP 6890/MSD 5973 fitted with a HP-5 column (30m × 0.25 mm × 0.25 μm). High-resolution mass spectra were recorded on a Finnigan-MAT 95Q spectrometer (electron impact, 70 eV). Microanalyses were performed using a Heraeus CHN Rapid Elementaranalysator. Flash column chromatographical purifications were carried out using Merck Kieselgel 60 (230–400 mesh ASTM).

Commercially available starting materials with a purity >97% were used without further purification. Solvents were distilled and dried before use. Starting material **1a,b** and **2** were prepared according to known methods.^{4,5}

3,3-Dibromo-2-phenylacrylic Acid Ethyl Ester (**1a**)⁴

A solution of CBr₄ (13.3 g, 40 mmol) in CH₂Cl₂ (15 mL) was added to a solution of Ph₃P (21.0 g, 80 mmol) in CH₂Cl₂ (20 mL) at 0 °C. After 30 min at 0 °C, a solution of ethyl phenylglyoxylate (**3a**; 3.56 g, 20 mmol) in CH₂Cl₂ (10 mL) was added. The mixture was warmed to 25 °C and stirred for 12 h, then added to pentane (70 mL), stirred for 30 min, filtered and concentrated. The crude residue was purified by flash chromatography (pentane–Et₂O, 3:1), yielding the product **1a** (3.94 g, 58%) as a yellow oil.

IR (film): 2982 (w), 1727 (s), 1204 cm^{−1} (s).

¹H NMR (300 MHz, CDCl₃): δ = 7.43–7.41 (m, 5 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 1.33 (t, *J* = 7.1 Hz, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 166.3, 142.0, 136.2, 129.4, 129.0, 128.5, 95.7, 62.6, 14.3.

MS: m/z (%) = 336 (6), 334 (12), 332 (5), 291 (5), 289 (12), 287 (5), 261 (15), 255 (33), 227 (21), 225 (23), 182 (49), 180 (51), 145 (100), 101 (54).

HRMS: m/z calcd for $C_{11}H_{10}Br_2O_2$: 331.9048; found: 331.9076.

3,3-Dibromo-2-methylacrylic Acid Methyl Ester (**1b**)⁴

A solution of CBr_4 (6.7 g, 20.1 mmol) in CH_2Cl_2 (10 mL) was added to a solution of Ph_3P (10.5 g, 40.2 mmol) in CH_2Cl_2 (40 mL) at 0 °C. After 30 min at 0 °C, a solution of methyl pyruvate (**3b**; 1.02 g, 10 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was warmed to r.t., stirred for 12 h, then added to pentane (70 mL), stirred for 30 min, filtered, and concentrated. The crude residue was purified by flash chromatography (pentane– Et_2O , 3:1) yielding the product **1b** (1.78 g, 69%) as a colorless oil.

IR (film): 2952 (w), 1732 (s), 1434 (m), 1285 (m), 1132 cm^{-1} (s).

1H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 2.07 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 134.9, 94.7, 51.9, 21.0.

MS: m/z (%) = 260 (19), 258 (44), 255 (22), 229 (39), 227 (91), 225 (42), 201 (16), 199 (32), 197 (17), 179 (100), 177 (100), 119 (24), 117 (24).

HRMS: m/z calcd for $C_5H_6Br_2O_2$: 255.8735; found: 255.8752.

3,3-Diiodo-2-phenylacrylic Acid Ethyl Ester (**2**)⁵

A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (9.1 mL, 44 mmol) in THF (20 mL) under argon. The reaction mixture was cooled to –10 °C and *n*-BuLi (29.3 mL, 44 mmol, 1.5 M in hexane) was added. The solution was stirred 30 min at –10 °C and then cooled to –70 °C. A solution of iodine (5.58 g, 22 mmol) in THF (20 mL) was added and then after 10 min, a solution of diethyl iodomethylphosphonate (6.11 g, 22 mmol) in THF (10 mL) was added. After 90 min at –70 °C, ethyl phenylglyoxylate (**3a**; 3.56 g, 20 mmol) in THF (5 mL) was added. The mixture was stirred 10 min at –70 °C then warmed up to r.t. After 2 h, H_2O (80 mL) was added and the aqueous solution was extracted with Et_2O . The combined organic layers were dried ($MgSO_4$) and concentrated. The crude residue was purified by flash chromatography (pentane– Et_2O , 9:1), yielding the product **2** (5.9 g, 70%) as a red oil.

IR (film): 3435 (w), 2924 (m), 1727 (s), 1442 (m), 1260 (s), 1196 cm^{-1} (s).

1H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.17 (m, 5 H), 4.11 (q, J = 7.1 Hz, 2 H), 1.16 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 153.4, 140.3, 129.4, 129.1, 128.2, 62.7, 20.0, 14.4.

MS: m/z (%) = 427 (30), 354 (10), 332 (100), 272 (48), 227 (62), 145 (80), 102 (61), 75 (40), 51 (44).

HRMS: m/z calcd for $C_{11}H_{10}I_2O_2$: 427.8770; found: 427.8818.

3-Bromo-3-iodo-2-phenylacrylic Acid Ethyl Ester (**5a**)

A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the dibromo ester **1a** (256 mg, 0.77 mmol) in Et_2O (4 mL) under argon. The reaction mixture was cooled to –50 °C and a 2 M solution of *i*-PrMgCl in Et_2O (0.42 mL, 0.84 mmol) was added dropwise. After stirring for 15 min at –50 °C, iodine (246 mg, 0.96 mmol) dissolved in Et_2O (4 mL) was added and the mixture was allowed to warm up to r.t. After 4 h, the mixture was quenched with brine (10 mL) and extracted with Et_2O . The organic layer was washed with an aq solution of $Na_2S_2O_3$, then brine, dried ($MgSO_4$) and concentrated under vacuum. The crude residue was purified by flash chromatography (pentane– Et_2O , 3:1), yielding the product **5a** (261 mg, 89%) as a yellow oil.

IR (film): 2981 (w), 1723 (s), 1443 (m), 1200 (s), 1036 cm^{-1} (m).

1H NMR (300 MHz, $CDCl_3$): δ = 7.30 (s, 5 H), 4.19 (q, J = 7.1 Hz, 2 H), 1.24 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 147.9, 136.8, 129.3, 129.0, 128.4, 62.7, 57.9, 14.4.

MS: m/z (%) = 382 (13), 380 (13), 255 (16), 227 (19), 225 (19), 182 (30), 180 (29), 145 (100), 101 (53).

HRMS: m/z calcd for $C_{11}H_{10}BrIO_2$: 379.8909; found: 379.8910.

3-Bromo-3-iodo-2-methylacrylic Acid Methyl Ester (**5b**)

A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the dibromo ester **1b** (252 mg, 0.98 mmol) in Et_2O (4 mL) under argon. The reaction mixture was cooled to –50 °C and a 2 M solution of *i*-PrMgCl in Et_2O (0.53 mL, 1.07 mmol) was added dropwise. After stirring for 15 min at –50 °C, iodine (357 mg, 1.4 mmol) dissolved in Et_2O (4 mL) was added and the mixture was allowed to warm up to r.t. After 4 h, the mixture was quenched with brine (10 mL) and extracted with Et_2O . The organic layer was washed with an aq solution of $Na_2S_2O_3$, then brine, dried ($MgSO_4$) and concentrated under vacuum. The crude residue was purified by flash chromatography (pentane– Et_2O , 3:1), yielding the product **5b** (268 mg, 89%) as a yellow oil.

IR (film): 2950 (w), 1728 (s), 1433 (m), 1252 (m), 1128 cm^{-1} (m).

1H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3 H), 2.00 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.2, 141.7, 57.2, 53.0, 22.2.

MS: m/z (%) = 306 (45), 304 (48), 275 (19), 273 (19), 179 (93), 177 (100), 127 (11).

HRMS: m/z calcd for $C_5H_6BrIO_2$: 303.8596; found: 303.8604.

Anal. Calcd for $C_5H_6BrIO_2$: C, 19.70; H, 1.98. Found: C, 19.92; H, 2.00.

4-Bromo-3,5-diphenyl-5H-furan-2-one (**6a**)

A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the dibromo ester **1a** (304 mg, 0.91 mmol) in Et_2O (4 mL) under argon. The reaction mixture was cooled to –50 °C and a 2 M solution of *i*-PrMgCl in Et_2O (0.5 mL, 1.00 mmol) was added dropwise. After stirring for 15 min at –50 °C, benzaldehyde (0.1 mL, 1.1 mmol) was added and the mixture was allowed to warm up to r.t. After 4 h, the mixture was quenched with brine (10 mL) and extracted with Et_2O . The organic layer was washed with brine, dried ($MgSO_4$) and concentrated under vacuum. The crude residue was purified by flash chromatography (pentane– Et_2O , 5:1), yielding the product **6a** (158 mg, 55%) as colorless crystals; mp 140 °C.

IR (film): 3487 (w), 1752 (s), 1634 (m), 1492 (m), 1294 (s), 1159 cm^{-1} (m).

1H NMR (300 MHz, $CDCl_3$): δ = 7.89–7.85 (m, 2 H), 7.55–7.35 (m, 8 H), 5.92 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 143.8, 133.7, 130.3, 129.9, 129.5, 129.1, 128.9, 127.9, 85.5.

MS: m/z (%) = 314 (4), 235 (100), 191 (23), 189 (22), 179 (33), 129 (13), 105 (100).

HRMS: m/z calcd for $C_{16}H_{11}BrO_2$: 313.9942; found: 313.9922.

Anal. Calcd for $C_{16}H_{11}BrO_2$: C, 60.98; H, 3.52; Br, 25.35. Found: C, 60.87; H, 3.51; Br, 25.78.

4-Bromo-3-methyl-5-phenyl-5H-furan-2-one (**6b**)

A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the dibromo ester **1b** (283 mg, 1.10 mmol) in Et_2O (4 mL) under argon. The reaction mixture was cooled to –50 °C and a 2 M solution of *i*-PrMgCl in Et_2O (0.6 mL, 1.20 mmol) was added dropwise. After stirring for 15 min at –50 °C, benzaldehyde (0.16 mL, 1.6 mmol) was added and the mixture was allowed

to warm up to r.t. After 4 h, the mixture was quenched with brine (10 mL) and extracted with Et₂O. The organic layer was washed with brine, dried (MgSO₄) and concentrated under vacuum. The crude residue was purified by flash chromatography (pentane–Et₂O, 3:1), yielding the product **6b** (157 mg, 56%) as a colorless oil.

IR (film): 3034 (w), 1766 (s), 1660 (m), 1456 (m), 1271 (m), 1088 cm⁻¹ (m).

¹H NMR (300 MHz, CDCl₃): δ = 7.35–7.30 (m, 3 H), 7.21–7.16 (m, 2 H), 5.68 (s, 1 H), 1.91 (s, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 171.5, 144.6, 133.6, 130.2, 129.3, 127.7, 85.6, 10.7.

MS: *m/z* (%) = 254 (20), 252 (21), 173 (100), 145 (10), 128 (22), 117 (14), 105 (48).

HRMS: *m/z* calcd for C₁₁H₉BrO₂: 251.9786; found: 251.9806.

Anal. Calcd for C₁₁H₉BrO₂: C, 52.20; H, 3.58. Found: C, 52.57; H, 3.62.

4-Bromo-3,5,5-triphenyl-5H-furan-2-one (7)

A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the dibromo ester **1a** (238 mg, 0.71 mmol) in Et₂O (4 mL) under argon. The reaction mixture was cooled to –50 °C and a 2 M solution of *i*-PrMgCl in Et₂O (0.4 mL, 0.78 mmol) was added dropwise. After stirring for 15 min at –50 °C, benzophenone (184 mg, 1.1 mmol) dissolved in Et₂O (4 mL) was added and the mixture was allowed to warm up to r.t. After 4 h, the mixture was quenched with brine (10 mL) and extracted with Et₂O. The organic layer was washed with brine, dried (MgSO₄) and concentrated under vacuum. The crude residue was purified by flash chromatography (pentane–Et₂O, 9:1), yielding the product **7** (222 mg, 79%) as a colorless oil.

IR (film): 3436 (m), 1762 (s), 1446 (m), 1171 cm⁻¹ (m).

¹H NMR (300 MHz, CDCl₃): δ = 7.76–7.72 (m, 2 H), 7.45–7.30 (m, 8 H).

¹³C NMR (75 MHz, CDCl₃): δ = 167.8, 146.6, 136.7, 129.5, 128.8, 128.2, 127.4, 127.2, 91.1.

MS: *m/z* (%) = 392 (2), 312 (100), 265 (51), 178 (21), 165 (34), 129 (12), 106 (16).

HRMS: *m/z* calcd for C₂₂H₁₅BrO₂: 390.0255; found: 390.0258.

Anal. Calcd for C₂₂H₁₅BrO₂: C, 67.53; H, 3.86. Found: C, 67.48; H, 4.23.

4-Bromo-3-phenyl-1-oxaspiro[4.4]non-3-en-2-one (8)

A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the dibromo ester **1a** (312 mg, 0.93 mmol) in Et₂O (4 mL) under argon. The reaction mixture was cooled to –50 °C and a 2 M solution of *i*-PrMgCl in Et₂O (0.51 mL, 1.03 mmol) was added dropwise. After stirring for 15 min at –50 °C, cyclopentanone (0.1 mL, 1.12 mmol) was added and the mixture was allowed to warm up to r.t. After 4 h, the mixture was quenched with brine (10 mL) and extracted with Et₂O. The organic layer was washed with brine, dried (MgSO₄) and concentrated under vacuum. The crude residue was purified by flash chromatography (pentane–Et₂O, 5:1), yielding the product **8** (195 mg, 71%) as a white solid; mp 138 °C.

IR (film): 3470 (w), 1739 (s), 1643 cm⁻¹ (w).

¹H NMR (300 MHz, CDCl₃): δ = 7.80–7.70 (m, 2 H), 7.51–7.42 (m, 3 H), 2.31–2.20 (m, 2 H), 2.11–1.90 (m, 6 H).

¹³C NMR (75 MHz, CDCl₃): δ = 167.3, 145.9, 127.9, 127.1, 126.8, 94.8, 35.6, 23.6.

MS: *m/z* (%) = 294 (1), 292 (1), 213 (100), 186 (9), 157 (28), 129 (43), 115 (19).

HRMS: *m/z* calcd for C₁₄H₁₃BrO₂: 292.0099; found: 292.0084.

4-(2-Oxo-3-phenyl-1-oxaspiro[4.4]non-3-en-4-yl)benzoic Acid Methyl Ester (11)

A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with 4-iodobenzoic acid methyl ester (**10**; 200 mg, 0.76 mmol) in THF (4 mL) under argon. The reaction mixture was cooled to –20 °C and a 1.6 M solution of *i*-PrMgCl in THF (0.52 mL, 0.84 mmol) was added dropwise. After stirring for 30 min at –20 °C, a 1.5 M solution of ZnBr₂ in THF (0.56 mL, 0.84 mmol) was added and the mixture was allowed to warm up to r.t. to give the zinc reagent **9**. Another dry two-necked flask equipped with a magnetic stirring bar and a septum under argon was charged with palladium(0) bis(dibenzylideneacetone) (14 mg, 5 mol%) and tris-*o*-furylphosphine (11 mg, 10 mol%) followed by THF (1 mL). The initial red color disappeared after 5 min leading to a yellow solution. The bromolactone **8** (150 mg, 0.51 mmol) was added, followed by the zinc reagent **9**. The reaction mixture was warmed to 30 °C and stirred for 10 h, worked up by pouring into aq sat. NaCl solution and extracted with Et₂O. The crude residue was purified by column chromatography on silica gel (pentane–Et₂O, 3:1) to give the spiro-lactone **11** (135 mg, 76%) as a white solid; mp 135 °C.

IR (film): 3480 (w), 2948 (w), 1752 (s), 1728 (s), 1435 (w), 1273 cm⁻¹ (m).

¹H NMR (300 MHz, CDCl₃): δ = 8.02–7.98 (m, 2 H), 7.36–7.12 (m, 7 H), 3.86 (s, 3 H), 2.05–1.60 (m, 8 H).

¹³C NMR (75 MHz, CDCl₃): δ = 171.3, 166.7, 162.2, 137.7, 131.1, 130.5, 130.4, 130.1, 129.7, 129.4, 129.2, 129.0, 128.8, 128.6, 128.5, 96.3, 52.7, 36.7, 24.8.

MS: *m/z* (%) = 348 (46), 319 (11), 291 (11), 261 (14), 243 (14), 203 (35), 185 (100), 157 (20).

HRMS: *m/z* calcd for C₂₂H₂₀O₄: 348.1362; found: 348.1356.

3-Isopropyl-2-phenylhexa-2,5-dienoic Acid Ethyl Ester (14a)

From Dibromo Ester 1a: A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the dibromo ester **1a** (230 mg, 0.68 mmol) in Et₂O (4 mL) under argon. The reaction mixture was cooled to –78 °C and a 2 M solution of *i*-PrMgCl in Et₂O (0.72 mL, 1.44 mmol) was added dropwise. After stirring for 15 min at –78 °C, then 3 h at 0 °C, a 1 M solution of CuCN·2LiCl in THF (0.01 mL, 0.01 mmol) was slowly added. After 5 min at 0 °C, allyl bromide (0.07 mL, 0.82 mmol) was added and the mixture was allowed to stir at 0 °C overnight. The mixture was quenched with brine (10 mL) and extracted with Et₂O. The organic layer was washed with brine, dried (MgSO₄) and concentrated under vacuum. The crude residue was purified by flash chromatography (pentane–Et₂O, 4:1), yielding the product **14a** (133 mg, 75%) as a colorless oil.

IR (film): 3417 (w), 2966 (m), 1715 (s), 1443 (m), 1236 cm⁻¹ (m).

¹H NMR (300 MHz, CDCl₃): δ = 7.30–7.10 (m, 5 H), 5.91–5.76 (m, 1 H), 5.08–4.92 (m, 2 H), 4.03 (q, *J* = 7.1 Hz, 2 H), 3.12 (dt, *J* = 6.3 Hz, *J* = 1.7 Hz, 2 H), 2.60–2.49 (m, 1 H), 1.10 (t, *J* = 7.1 Hz, 3 H), 0.87 (d, *J* = 6.8 Hz, 6 H).

¹³C NMR (75 MHz, CDCl₃): δ = 168.7, 151.9, 137.5, 129.2, 128.2, 127.1, 115.4, 60.5, 32.3, 20.8, 14.1.

MS: *m/z* (%) = 258 (8), 217 (22), 189 (13), 185 (82), 169 (25), 143 (100), 128 (54), 115 (38), 91 (34).

HRMS: *m/z* calcd for C₁₇H₂₂O₂: 258.1620; found: 258.1604.

3-Isopropyl-2-phenylhexa-2,5-dienoic Acid Ethyl Ester (14a)

From Diiodo Ester 2: A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the diiodo ester **2** (191 mg, 0.44 mmol) in THF (4 mL) under argon. The reaction mix-

ture was cooled to $-78\text{ }^{\circ}\text{C}$ and a 1.7 M solution of *i*-PrMgCl in THF (0.55 mL, 0.93 mmol) was added dropwise. After stirring 5 min at $-78\text{ }^{\circ}\text{C}$, then 2 h at $-10\text{ }^{\circ}\text{C}$, a 1 M solution of CuCN·2LiCl in THF (0.04 mL, 0.04 mmol) was slowly added. After 5 min at $-10\text{ }^{\circ}\text{C}$, allyl bromide (0.04 mL, 0.5 mmol) was added and the mixture was allowed to stir at $-10\text{ }^{\circ}\text{C}$ overnight. The mixture was quenched with brine (10 mL) and extracted with Et₂O. The organic layer was washed with brine, dried (MgSO₄) and concentrated under vacuum. The crude residue was purified by flash chromatography (pentane–Et₂O, 4:1), yielding a *E/Z* mixture of **14** (determined by GC-MS and NMR, (*E/Z*)-**14a** = 1:9, 89 mg, 78%) as a colorless oil.

3-Isobutyl-2-phenylhexa-2,5-dienoic Acid Ethyl Ester (14b)

A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the dibromo ester **1a** (216 mg, 0.65 mmol) in Et₂O (4 mL) under argon. The reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and a 2 M solution of *i*-BuMgCl in Et₂O (0.68 mL, 1.35 mmol) was added dropwise. After stirring 15 min at $-78\text{ }^{\circ}\text{C}$, then 4 h at $0\text{ }^{\circ}\text{C}$, a 1 M solution of CuCN·2LiCl in THF (0.06 mL, 0.06 mmol) was slowly added. After 5 min at $0\text{ }^{\circ}\text{C}$, allyl bromide (0.06 mL, 0.77 mmol) was added and the mixture was allowed to stir at $0\text{ }^{\circ}\text{C}$ overnight. The mixture was quenched with brine (10 mL) and extracted with Et₂O. The organic layer was washed with brine, dried (MgSO₄) and concentrated under vacuum. The crude residue was purified by flash chromatography (pentane–Et₂O, 50:3), yielding the product **14b** (128 mg, 73%) as a colorless oil.

IR (film): 3412 (w), 2957 (m), 1715 (s), 1464 (m), 1236 cm⁻¹ (s).

¹H NMR (400 MHz, CDCl₃): δ = 7.34–7.24 (m, 3 H), 7.21–7.17 (m, 2 H), 5.96–5.85 (m, 1 H), 5.16–5.06 (m, 2 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 3.18 (d, *J* = 6.7 Hz, 2 H), 1.91 (d, *J* = 7.0 Hz, 2 H), 1.88–1.76 (m, 1 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 0.75 (d, *J* = 6.4 Hz, 6 H).

¹³C NMR (100 MHz, CDCl₃): δ = 168.8, 146.3, 137.7, 136.0, 132.6, 129.7, 128.0, 127.0, 116.2, 60.5, 41.2, 37.3, 26.4, 22.5, 14.1.

MS: *m/z* (%) = 272 (4), 227 (10), 211 (18), 199 (87), 169 (26), 155 (63), 143 (100), 129 (42), 115 (53), 91 (17).

HRMS: *m/z* calcd for C₁₈H₂₄O₂: 272.1776; found: 272.1765.

3-Iodo-4-methyl-2-phenylpent-2-enoic Acid Ethyl Ester (15)

A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the dibromo ester **1a** (205 mg, 0.61 mmol) in Et₂O (4 mL) under argon. The reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and a 2 M solution of *i*-PrMgCl in Et₂O (0.72 mL, 1.44 mmol) was added dropwise. After stirring for 15 min at $-78\text{ }^{\circ}\text{C}$, then 3 h at $0\text{ }^{\circ}\text{C}$, a solution of iodine (342 mg, 1.34 mmol) in Et₂O (4 mL) was added and the mixture was allowed to warm up to r.t. overnight. The mixture was quenched with brine (10 mL) and extracted with Et₂O. The organic layer was washed with aq sat. solution of Na₂S₂O₃ and then brine, dried (MgSO₄) and concentrated under vacuum. The crude residue was purified by flash chromatography (pentane–Et₂O, 5:1), yielding the product **15** (172 mg, 82%) as a colorless oil.

IR (film): 3432 (w), 2966 (s), 1727 (s), 1614 (m), 1443 (m), 1266 (s), 1201 cm⁻¹ (s).

¹H NMR (300 MHz, CDCl₃): δ = 7.30–7.19 (m, 5 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 2.12–2.02 (m, 1 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 0.87 (d, *J* = 6.4 Hz, 6 H).

¹³C NMR (75 MHz, CDCl₃): δ = 169.0, 141.3, 136.5, 129.1, 128.6, 128.5, 121.9, 89.1, 62.0, 34.7, 23.9, 14.4.

MS: *m/z* (%) = 344 (3), 217 (44), 189 (24), 171 (31), 143 (100), 128 (80), 115 (14), 77 (13).

HRMS: *m/z* calcd for C₁₄H₁₇IO₂: 344.0273; found: 344.0341.

3-Benzoyl-4-methyl-2-phenylpent-2-enoic Acid Ethyl Ester (16)

A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the dibromo ester **1a** (210 mg, 0.63 mmol) in Et₂O (4 mL) under argon. The reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and a 2 M solution of *i*-PrMgCl in Et₂O (0.66 mL, 1.32 mmol) was added dropwise. After stirring for 15 min at $-78\text{ }^{\circ}\text{C}$, then 3 h at $0\text{ }^{\circ}\text{C}$, a 1 M solution of CuCN·2LiCl in THF (0.66 mL, 0.66 mmol) was slowly added. After 5 min at $0\text{ }^{\circ}\text{C}$, benzoyl chloride (0.1 mL, 0.75 mmol) was added and the mixture was allowed to stir at $0\text{ }^{\circ}\text{C}$ overnight. The mixture was quenched with brine (10 mL) and extracted with Et₂O. The organic layer was washed with brine, dried (MgSO₄) and concentrated under vacuum. The crude residue was purified by flash chromatography (pentane–Et₂O, 3:1), yielding the product **16** (124 mg, 61%) as a colorless oil.

IR (film): 2972 (m), 1712 (s), 1670 (s), 1596 (m), 1448 (m), 1290 cm⁻¹ (s).

¹H NMR (300 MHz, CDCl₃): δ = 7.97–7.92 (m, 2 H), 7.53–7.25 (m, 8 H), 3.78 (q, *J* = 7.1 Hz, 2 H), 2.78–2.64 (m, 1 H), 0.90 (d, *J* = 7.1 Hz, 6 H), 0.80 (t, *J* = 7.1 Hz, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 197.5, 166.5, 157.4, 137.8, 135.9, 133.4, 132.2, 129.7, 129.0, 128.9, 128.7, 128.2, 61.6, 32.1, 21.6, 13.9.

MS: *m/z* (%) = 322 (4), 276 (100), 217 (15), 143 (20), 105 (90), 77 (50).

HRMS: *m/z* calcd for C₂₁H₂₂O₃: 322.1569; found: 322.1581.

4-Isopropyl-3,5-diphenyl-5H-furan-2-one (17)

A dry two-necked flask equipped with a magnetic stirring bar and a septum was charged with the dibromo ester **1a** (214 mg, 0.64 mmol) in Et₂O (4 mL) under argon. The reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and a 2 M solution of *i*-PrMgCl in Et₂O (0.67 mL, 1.34 mmol) was added dropwise. After stirring for 15 min at $-78\text{ }^{\circ}\text{C}$, then 3 h at $0\text{ }^{\circ}\text{C}$, benzaldehyde (0.08 mL, 0.77 mmol) was added and the mixture was allowed overnight to warm up to r.t. The mixture was quenched with brine (10 mL) and extracted with Et₂O. The organic layer was washed with brine, dried (MgSO₄) and concentrated under vacuum. The crude residue was purified by flash chromatography (pentane–Et₂O, 3:1), yielding the product **17** (100 mg, 56%) as a colorless oil.

IR (film): 3491 (w), 2970 (m), 1755 (s), 1445 (m), 1132 cm⁻¹ (m).

¹H NMR (300 MHz, CDCl₃): δ = 7.40–7.32 (m, 8 H), 7.27–7.19 (m, 2 H), 5.83 (s, 1 H), 2.99–2.96 (m, 1 H), 1.03 (d, *J* = 7.1 Hz, 3 H), 0.67 (d, *J* = 7.1 Hz, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 173.5, 169.3, 135.8, 130.7, 129.9, 129.7, 129.3, 129.0, 128.9, 128.0, 127.0, 83.4, 28.5, 22.1, 21.3.

MS: *m/z* (%) = 278 (2), 235 (100), 179 (10), 129 (8), 105 (30), 77 (5).

HRMS: *m/z* calcd for C₁₉H₁₈O₂: 278.1307; found: 278.1300.

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References

- (1) (a) Mueller, A.; Marsch, M.; Harms, K.; Lohrenz, J. C. W.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1518. (b) Hoffmann, R. W.; Julius, M.; Chemla, F.; Ruhland, T.; Frenzen, G. *Tetrahedron* **1994**, *50*, 6049. (c) Villieras, J.; Kirschleger, B.; Tarhouni, R.; Rambaud, M. *Bull. Soc. Chim. Fr.* **1986**, 470.
- (2) (a) Avolio, S.; Malan, C.; Marek, I.; Knochel, P. *Synlett* **1999**, 1820. (b) Vu, V. A.; Marek, I.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 351. (c) Shibli, A.; Varghese, J. P.; Knochel, P.; Marek, I. *Synlett* **2001**, 818.
- (3) (a) Rottländer, M.; Boymond, L.; Bérillon, L.; Leprêtre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Quéguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem.–Eur. J.* **2000**, *6*, 767. (b) Kopp, F.; Sapountzis, I.; Knochel, P. *Synlett* **2003**, 885. (c) Staubitz, A.; Dohle, W.; Knochel, P. *Synthesis* **2003**, 233. (d) Kneisel, F. F.; Knochel, P. *Synlett* **2002**, 1799. (e) Gommermann, N.; Koradin, K.; Knochel, P. *Synthesis* **2002**, 2143. (f) Bonnet, V.; Mongin, F.; Trecourt, F.; Breton, G.; Marsais, F.; Knochel, P.; Quéguiner, G. *Synlett* **2002**, 1008. (g) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, 565. (h) Varchi, G.; Jensen, A. E.; Dohle, W.; Ricci, A.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 477.
- (4) Colson, P. J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 5918.
- (5) (a) Bonnet, B.; Le Gallic, Y.; Plé, G.; Duhamel, L. *Synthesis* **1993**, 1071. (b) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.
- (6) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.
- (7) (a) Rottländer, M.; Knochel, P. *J. Org. Chem.* **1998**, *63*, 203. (b) Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G. *Tetrahedron* **1996**, *52*, 7201.
- (8) (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. (b) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.
- (9) (a) Negishi, E.; Akiyoshi, K. *J. Am. Chem. Soc.* **1988**, *110*, 646. (b) Miller, J. A. *J. Org. Chem.* **1989**, *54*, 998. (c) Harada, T.; Katsuhira, T.; Hattori, K.; Oku, A. *Tetrahedron Lett.* **1989**, *30*, 6039. (d) Knochel, P.; Jeong, N.; Rozema, M. J.; Yeh, M. C. P. *J. Am. Chem. Soc.* **1989**, *111*, 6474. (e) Knochel, P.; Rao, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 6146. (f) Harada, T.; Kotani, Y.; Katsuhira, T.; Oku, A. *Tetrahedron Lett.* **1991**, *32*, 1573. (g) Harada, T.; Katsuhira, T.; Hara, D.; Kotani, Y.; Maejima, K.; Kaji, R.; Oku, A. *J. Org. Chem.* **1993**, *58*, 4897. (h) Hata, T.; Kitagawa, H.; Masai, H.; Kurahashi, T.; Shimizu, M.; Hiyama, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 790. (i) Kurahashi, T.; Hata, T.; Masai, H.; Kitagawa, H.; Shimizu, M.; Hiyama, T. *Tetrahedron* **2002**, *58*, 6381.
- (10) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.