Dimethyl Phosphite Mediated Hydrogen Atom Abstraction: A Novel Tin-Free Procedure for the Preparation of Cyclopentane Derivatives

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General techniques. Flash column chromatography (FC) and filtration: *Baker* silica gel (0.063-0.200 mm); AcOEt and cyclohexane as eluents. IR spectroscopy: *Perkin-Elmer FT IR 1615*. NMR spectroscopy: *Bruker AC 300* (1H = 300 MHz, 13C = 75.5 MHz); chemical shift in ppm relative to tetramethylsilane (δ = 0 ppm) or CHCl3 for 1H (δ = 7.26 ppm) and CDCl3 for 13C (δ = 77.16 ppm). MS: *Micromass AutospecQ (Manchester, UK)*; EI (70 eV) m/z (%). High resolution mass spectra (HRMS) were recorded on a *Micromass AutospecQ* as LSIMS (Liquid Secondary Ion Mass Spectr.) with a Cs+ ion beam at 20KV (polyethyleneglycol as internal standard). GC/MS: *Instrument Finnigan Trace GC/MS* (quadrupole mass analyzer). GC-column: *Macharey-Nagel optima delta 3* (autoselective stationary phase, non-polar to medium polarity). Length 30 m; internal diameter 0.25 mm; thickness of stationary phase 0.25 µm; Injection volume: 1 µL; Injector temperature: 250°C; Carrier gas: Helium; Standard temperature program: 40°C, 1 min., 40°C ⇒ 280°C, 6°C/min., 280°C, 30 min.; Ionization: electron impact (EI), 70 eV; Ion source temperature: 250°C; Mass range: m/z 33-450, or m/z 180-600, depending on sample. GC: *Instrument Shimadzu*. GC-column: *Macharey-Nagel optima delta 3* (autoselective stationary phase, non-polar to medium polarity). Length 10 m; internal diameter 0.25 mm; thickness of stationary phase 0.25 µm; Carrier gas: Helium; Standard temperature program: 100°C - 280°C, 15°C/min., 280°C, 30 min.

**General procedure for radical reaction using dimethyl phosphite GP1.** A mixture of malonate (1 mmol, 0.1M in cyclohexane), dilauroyl peroxide (1 mmol, 398 mg) and dimethyl phosphite (5 mmol, 550 mg) in cyclohexane (10 mL) was heated at 80 °C for 6 h. After completion (GC monitoring), the solution was cooled and cyclohexane evaporated under reduced pressure. CH3CN (10 mL) was added and the precipitate removed by filtration. Then the residue was purified by flash chromatography to afford the desired cyclic compounds. The ratio of the isomers was determined by GC-MS analyses realized on the crude reaction mixture.

**General procedure for radical reaction using dimethyl phosphite GP2.** A mixture of malonate (1 mmol, 0.1M in cyclohexane), dibenzoyl peroxide (1 mmol, 242 mg) and dimethyl phosphite (5 mmol, 550 mg) in cyclohexane (10 mL) was heated at 80 °C for 6 h. After completion (GC monitoring), the solution was cooled and cyclohexane evaporated under reduced pressure. Dimethyl phosphite was removed by distillation (Kugelrohr: 100°C, 1 mBar, 15 min). Then the residue was filtered through silica gel (5 g) (hexane/tert-BuOMe...
2:1, then AcOEt) to afford the desired cyclic compounds. The ratio of diastereomers was determined by GC-MS analysis of crude reaction mixtures.

3-(Dimethoxyphosphoryl-methyl)-4-ethylcyclopentane-1,1-dicarboxylic acid diethyl ester 2a. According to the general procedure GP1, from 1a (254 mg, 1 mmol). FC (AcOEt/cyclohexane 80:20) gave 2a (295 mg, 81%) as a 69:31 mixture of diastereomers. Retention time of the diastereomers (major/minor) determined by GC analysis : 9.96/9.75. **Major isomer.** $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.18 (q, $J = 7.2$ Hz, 4H), 3.75 (d, $J = 10.7$ Hz, 3H), 3.74 (d, $J = 10.9$ Hz, 3H), 2.58-2.38 (m, 2H), 2.27 (dd, $J = 13.1$, 6.2 Hz, 1H), 2.16 (dd, $J = 13.1$, 6.3 Hz, 1H), 2.05-1.48 (m, 4H), 1.40-1.21 (m, 1H), 1.24 (t, $J = 7.1$ Hz, 6H), 1.13-0.93 (m, 1H), 0.90 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (300 MHz, CDCl$_3$) $\delta$ 173.0, 172.8, 61.6, 58.7, 52.5 (d, $J = 6.8$ Hz), 52.3 (d, $J = 6.2$ Hz), 44.8 (d, $J = 13.6$ Hz), 39.3 (d, $J = 5.6$ Hz), 37.9, 36.4 (d, $J = 5.0$ Hz), 24.3 (d, $J = 140$ Hz), 21.9, 14.1, 12.6. $^{31}$P NMR (75 MHz, CDCl$_3$) $\delta$ 34.83. IR (cm$^{-1}$) film ν 2957, 1725, 1463, 1366, 1246, 1179, 1094, 1024, 815, 723. ES (MS) 363 (M-H$^+$, 5), 348 (2), 334 (20), 319 (40), 291 (10), 262 (10), 255 (10), 245 (50), 241 (40), 218 (20), 217 (40), 215 (25), 209 (10), 192 (50), 181 (15), 167 (20), 151 (60), 137 (15), 135 (45), 125 (65), 124 (100), 111 (10), 110 (20), 109 (20), 107 (65), 94 (55), 91 (15), 79 (50), 67 (15), 55 (10), 41 (15). HRMS for C$_{16}$H$_{30}$O$_3$P [MH$^+$]: calcd 365.1729, found 365.1725.

4-(Dimethoxyphosphoryl-methyl)-3,3-dimethylcyclopentane-1,1-dicarboxylic acid dimethyl ester 2b. According to the general procedure GP1, from 1b (226 mg, 1.00 mmol). FC (AcOEt/cyclohexane 80:20) gave 2b (306 mg, 91 %). Retention time of the determined by GC/MS analysis: 33.17.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.76 (d, $J = 11.0$ Hz, 3H, P-OME), 3.74 (d, $J = 11.0$ Hz, 3H, P-O-Me), 3.71 (s, 6H), 2.68 (dd, $J = 13.6$, 7.0 Hz, 1H), 2.27 (dd, $J = 14.0$, 1.5 Hz, 1H), 2.16-2.10 (m, 1H), 2.12 (dd, $J = 14.0$, 7.0 Hz, 1H), 2.02-1.89 (m, 1H), 1.75-1.89 (m, 1H), 1.58-1.43 (m, 1H), 1.01 (s, 3H), 0.74 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.3, 173.1, 173.1, 57.5, 52.9, 52.8, 52.6 (d, $J = 6.8$ Hz), 52.3 (d, $J = 6.2$ Hz), 48.1, 43.2 (d, $J = 5.0$ MHz), 42.0 (d, $J = 16.7$ Hz), 39.3, 27.1, 24.7 (d, $J = 140.7$ Hz), 21.6. $^{31}$P (300 MHz, CDCl$_3$) $\delta$ 34.53. IR (cm$^{-1}$) film ν 2954, 1730, 1434, 1370, 1250, 1210, 1154, 1053, 1025, 917, 869, 842, 816, 727. EI (MS) m/z (%): 336 (M$^+$, 20), 321 (70), 305 (60), 280 (15), 277 (10), 261 (10), 248 (20), 245 (40), 229 (35), 217 (30), 192 (70), 186 (30), 173 (20), 167 (34), 151 (98), 137 (25), 135 (50), 124 (100), 122 (35), 110 (65), 109 (58), 107 (70), 93 (60), 79 (40), 67 (15), 59 (20), 47 (10), 41 (35). HRMS for C$_{16}$H$_{32}$O$_6$PNa [MNa$^+$]: calcd 539.1235, found 539.1235.

4-(Dimethoxyphosphoryl-methyl)-cyclopentane-5-Isopropyl-1,1,3-tricarboxylic acid 3-ethyl ester 1,1-dimethyl ester 2c. According to the general procedure GP1, from 1c (312 mg, 1.00 mmol). FC (AcOEt/cyclohexane 80:20) gave 2c (384 mg, 91%) as a 82:18 mixture of diastereomers. Retention time of the diastereomers (major/minor) determined by GC/MS analysis: 38.20/38.20. Ratio determined by $^{31}$P.
3-(Dimethoxycarbonyl-methyl)-4-phenyl-cyclopentane-1,1-dicarboxylic acid dimethyl ester 2d. According to the general procedure GP1, from 1d (274 mg, 1.00 mmol). FC (AcOEt/cyclohexane 80:20) gave 2d (211 mg, 55%) as a 73:27 mixture of diastereomers. Retention time of the diastereomers (major/minor) determined by GC analysis: 11.99/12.01

Major isomer. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.40-7.29 (m, 2H), 7.29-7.12 (m, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.60 (d, \(J = 10.8\) Hz, 3H), 3.57 (d, \(J = 10.8\) Hz, 3H), 2.81 (dd, \(J = 13.9, 7.3\) Hz, 1H), 2.79-2.60 (m, 2H), 2.43-2.23 (m, 2H), 2.03 (dd, \(J = 13.7, 10.8\) Hz, 1H), 1.77 (ddd, \(J = 19.6, 15.3, 2.7\) Hz, 1H), 1.70-1.49 (ddd, \(J = 17.2, 15.3, 11.1\) Hz, 1H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 172.9, 172.8, 140.6, 128.8 (2C), 127.1, 58.2, 53.3, 53.1, 52.9, 52.3 (d, \(J = 6.8\) Hz), 52.1 (d, \(J = 6.2\) Hz), 42.0, 41.4 (d, \(J = 5\) Hz), 40.4, 27.7 (d, \(J = 140\) Hz), \(^{31}\)P NMR (300 MHz, CDCl\(_3\)) \(\delta\) 33.02. IR (cm\(^{-1}\)): 2953, 2855, 1732, 1461, 1435, 1249, 1196, 1097, 1055, 1027, 976, 776, 728. EI (MS) m/z (%): 384 (M\(^+\), 45), 382 (30), 353 (30), 322 (30), 293 (20), 292 (15), 291 (10), 265 (10), 261 (10), 240 (10), 238 (5), 216 (5), 201 (10), 200 (5), 183 (15), 182 (10), 181 (5), 169 (5), 155 (35), 153 (25), 141 (10), 128 (10), 125 (60), 124 (100), 115 (20), 109 (10), 104 (10), 94 (50), 91 (15), 79 (10), 59 (5), 44 (5). HRMS for C\(_{18}\)H\(_{25}\)O\(_7\)P \([M^+\]): calcd 384.1337, found 384.1336.

3-(tert-Butyl-dimethyl-silanoxy)-4-(dimethoxycarbonyl-methyl)-cyclopentane-1,1-dicarboxylic acid dimethyl ester 2e. According to the general procedure GP1, from 1e (328 mg, 1.00 mmol). FC (AcOEt/cyclohexane 80:20) gave 2e (346 mg, 79%) as a 76:24 mixture of diastereomers. Retention time of the diastereomers (major/minor) determined by GC analysis: 10.68/10.81.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (major isomer) 3.73 (d, \(J = 10.9\) Hz, 3H), 3.72 (d, \(J = 10.9\) Hz, 3H), 3.71 (s, 3H), 3.72-3.68 (m, 1H), 3.70 (s, 3H), 2.83 (dd, \(J = 14.1, 7.5\) Hz, 1H), 2.55 (dd, \(J = 13.4, 6.2\) Hz, 1H), 2.16-1.96 (m, 3H), 1.70 (dd, \(J = 14.1, 9.6\) Hz, 1H), 1.62-1.42 (m, 1H), 0.85 (s, 9H), 0.04 (s, 6H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) (major isomer) 173.1, 172.3, 56.3, 53.0, 52.9, 52.6, 52.5, 52.4, 52.3, 41.7 (d, \(J = 5\) Hz), 41.4, 36.8, 36.7, 27.6 (d, \(J = 141.4\)Hz), 25.8, 18.0, -4.4, -4.7. \(^{31}\)P NMR (300 MHz, CDCl\(_3\)) \(\delta\) (major isomer) 33.02. IR (cm\(^{-1}\)) v 2953, 2855, 1732, 1461, 1435, 1249, 1196, 1097, 1055, 1027, 925, 845, 835, 776, 728. EI (MS) m/z (%): 438 (M\(^+\), 2), 409 (5), 408 (12), 407 (45), 384 (20), 383 (65), 382 (85), 381 (100), 347 (5), 331 (5), 321 (15), 315 (20), 291 (10), 289 (15), 263 (10), 256 (5), 237 (10), 229 (10), 223 (35), 215 (50), 199 (25), 183 (10), 179 (10), 167 (40), 151 (25), 137 (35), 124 (50), 109 (30), 105 (60), 94 (25), 89 (65), 79 (25), 75 (50), 73 (75), 59 (60). HRMS for C\(_{18}\)H\(_{36}\)O\(_8\)PSi \([M^+\]): calcd 439.1917, found 439.1912.

2-(3-Oxo-cyclopentyl)-2-prop-2-ynyl-malonic acid dimethyl ester 3a. To a solution of dimethyl propargylmalonate (0.82 mL, 6.0 mmol) in THF (6 mL) were added cyclopenten-2-one (0.50 mL, 6.0 mmol) and DBU (0.9 mL, 6.0 mmol) at room temperature. After stirring at room temperature for 10 h, the mixture was concentrated under reduce pressure. The residue was purified by flash chromatography (hexane/EtOAc 2:1) to give 3a (1.06 g, 70%) as a colorless oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.77 (s, 6H), 3.05-3.12 (m, 1H), 2.83 (qd, 2H, \(J = 2.69, 17.12\)), 2.57 (dd, 1H, \(J = 7.58, 18.34\)), 2.15-2.37 (m, 4H), 2.07 (t, 1H, \(J = 2.69\)), 1.70 (m, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 23.8 (CH\(_2\)), 25.0 (CH\(_2\)), 38.5 (CH\(_3\)), 39.6 (CH), 41.0 (CH\(_2\)), 52.8 (2 x CH\(_3\)), 59.0 (C), 71.9 (CH), 78.4 (C), 169.7 (C), 169.8 (C), 217.1 (C). IR (cm\(^{-1}\))
2-(3-Oxo-cyclohexyl)-2-prop-2-ynyl-malonic acid dimethyl ester 3b. To a solution of dimethyl propargylmalonate (1.64 mL, 12.0 mmol) in THF (12 mL) were added cyclohexen-2-one (1.15 mL, 12.0 mmol) and DBU (1.8 mL, 12.0 mmol) at room temperature. After stirring at rt for 10 h, the mixture was concentrated under reduce pressure. The residue was purified by flash chromatography (hexane/EtOAc 2:1) to give 3b (2.46 g, 77%) as a colorless oil.

1H NMR (300MHz, CDCl₃) δ 3.78 (s, 6H), 2.89 (d, 2H, J = 2.45), 2.63-2.72 (m, 1H), 2.53-2.59 (m, 1H), 2.39-2.47 (m, 1H), 2.19-2.31 (m, 2H), 2.05-2.15 (m, 2H), 2.07 (t, 1H, J = 2.4Hz), 1.59-1.72 (m, 1H), 1.38-1.48 (m, 1H).

13C NMR (100 MHz, CDCl₃) δ 22.9 (CH₂), 24.6 (CH₂), 27.1 (CH₂), 40.9 (CH₂), 41.0 (CH), 43.4 (CH₂), 52.7 (CH₃), 52.8 (CH₃), 59.9 (C), 71.9 (CH), 78.6 (C), 169.6 (C), 169.7 (C), 209.9 (C). IR (cm⁻¹) ν 3280, 2954, 1731, 1435, 1372, 1236, 1108, 1045, 979. EI (MS) m/z (%): 267 (M+H⁺, 8), 172 (13), 171 (100), 139 (78), 111 (59). HRMS for C₁₃H₁₉O₅ [M+H⁺]: calcd 267.1229, found 267.1232.

3-(Dimethoxyphosphoryl-methyl)-4-oxo-hexahydro-pentalene-1,1-dicarboxylic acid dimethyl ester 4a. According to the general procedure GP1, from 3a (252 mg, 1.00 mmol). Flash chromatography  (AcOEt/cyclohexane 80/20) gave 4a (257 mg, 71%) as a 85:15 mixture of diastereomers. Retention time of the diastereomer (major/minor) determined by GC analysis : 11.59/11.59. Ratio determined by 31P. Major isomer.

1H NMR (300 MHz, CDCl₃) δ 3.76 (s, 3H), 3.75 (s, 3H), 3.73 (d, J = 10.9 Hz, 3H), 3.72 (d, J = 10.9 Hz, 3H), 3.63-3.45 (m, 1H), 2.83 (t, J = 9.4 Hz, 1H), 2.65-2.37 (m, 3H), 2.29-2.16 (m, 2H), 2.15-1.92 (m, 2H), 1.55-1.36 (m, 2H).

13C NMR (75 MHz, CDCl₃) δ 219.0, 171.8, 170.0, 64.1, 53.2, 53.0 (d, J = 14.3 Hz), 52.7, 52.5 (d, J = 6.8 Hz), 52.3 (d, J = 6.8 Hz), 46.2, 39.6, 39.4 (d, J = 4.3 Hz), 34.2 (d, J = 3.7 Hz), 25.9 (d, J = 140.1 Hz), 24.2. 31P NMR (300 MHz, CDCl₃) δ 32.97. IR (cm⁻¹) ν 2954, 1725, 1435, 1241, 1098, 1018, 959, 797, 696. EI (MS) m/z (%): 267 (M+H⁺, 8), 172 (13), 171 (100), 139 (78), 111 (59). HRMS for C₁₅H₂₄O₈P [MH⁺]: calcd 363.1208, found 363.1198.

3-(Diethoxyphosphoryl-methyl)-4-o xo-octahydro-1H-indene-1,1-dicarboxylate 4b. According to the general procedure GP2, from 3b (266 mg, 1.00 mmol). FC (AcOEt) gave 4b (380 mg, 94%) as a 56:44 mixture of diastereomers. IR (cm⁻¹) ν 2952, 1727, 1434, 1391, 1241, 1098, 1018, 959, 797, 696. EI (MS) m/z (%): 404 (21), 373 (13), 345 (25), 313 (44), 260 (98), 185 (30), 152 (67), 138 (42), 125 (52), 111 (85), 91 (60), 83 (100), 65 (81), 45 (41). HRMS for C₁₈H₂₉O₈P [M⁺]: calcd 404.1600, found 404.1601.

3-(Dimethoxyphosphoryl-methyl)-hexahydro-pentalene-1,1-dicarboxylic acid dimethyl ester 4c. According to the general procedure GP1, from 3c (238 mg, 1.00 mmol). FC (AcOEt/cyclohexane 80:20) gave 4c (323 mg, 93%) as a 92:8 mixture of diastereomers. Retention time of the diastereomers (major/minor) determined by GC/MS analysis: 37.16/36.69.
2-Oxo-1-pent-4-ynyl-cyclopentanone carboxylic acid methyl ester. To a suspension of sodium hydride (0.52 g, 12 mmol, 55 - 65% dispersion in mineral oil) in DMF (10 mL) was added dropwise at 0°C a solution of 2-oxo-cyclopentanecarboxylic acid methyl ester (1.42 g, 10 mmol) in DMF (10 mL). The cold bath was removed and the reaction mixture stirred at room temperature for 1.5 h. A solution of 5-iodo-pent-1-yne (1.94 g, 10 mmol) in DMF (10 mL) was added dropwise at room temperature and the reaction mixture was stirred for 12 h. The reaction was treated with 1N HCl. tert-BuOMe (20 mL) was added and the aqueous layer extracted with tert-BuOMe (4 x). The combined organic layers were washed with HCl (1N), brine (2 x), dried over Na₂SO₄, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane/tert-BuOMe 95:5) to give the desired compound (1.25 g, 60%) as a pale yellow oil.

1H NMR (400 MHz) δ 3.69 (s, 3H), 2.57-2.50 (m, 1H), 2.45 -2.37 (m, 1H), 2.30 -2.16 (m, 3H), 2.06 -1.85 (m, 5H), 1.70 -1.52 (m, 2H), 1.49 -1.38 (m, 1H). 13C NMR (100 MHz) δ 214.7, 171.5, 83.8, 68.9, 60.3 (Cq), 52.7, 38.0, 33.2, 33.0, 24.1, 18.8. IR (cm⁻¹) film ν 3282, 2953, 2363, 2116, 1747, 1718, 1433, 1405, 1258, 1228, 1145, 1115, 993, 917, 838, 650. EI (MS) m/z (%): 209 (MH⁺, 0.1), 193 (0.4), 180 (5), 177 (10), 165 (5), 152 (10), 151 (35), 149 (28), 148 (29), 142 (50), 139 (14), 133 (5), 131 (13), 121 (75), 120 (50), 110 (35), 107 (39), 106 (100), 105 (25), 93 (82), 91 (80), 81 (33), 79 (45), 77 (60), 67 (53), 65 (15), 59 (30), 55 (35), 53 (35), 41 (37), 39 (25). HRMS for C₁₂H₁₆O₃ [M⁺]: calcd 208.1099, found 208.1103.

2-Pent-4-ynyl-cyclopentanone 5a. To a solution of 2-oxo-1-pent-4-ynyl-cyclopentane carboxylic acid methyl ester (624 mg, 3.00 mmol) in DMF (4 mL) was added LiI (2.00 g, 15 mmol). The reaction mixture was stirred at 150 °C for 1.5 h. After completion (GC analysis), the reaction mixture was cooled at room temperature and treated with 1N HCl. tert-BuOMe (20 mL) was added and the aqueous layer extracted with tert-BuOMe (4 x). The combined organic layers were washed with 1N HCl, brine (2 x), dried over Na₂SO₄, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane/tert-BuOMe 90:10) to give 1.00 g (365 mg, 81%) as a pale yellow oil.

1H NMR (400 MHz) δ 2.33-1.96 (m, 6H), 1.94 (t, J = 2.6 Hz, 1H), 1.90 -1.71 (m, 2H), 1.64 -1.47 (m, 3H), 1.41-1.32 (m, 1H). 13C NMR (100 MHz) δ 221.2, 84.2, 68.7, 48.8 (CH), 38.2, 29.8, 29.0, 26.7, 20.9, 18.6. IR (cm⁻¹) film ν 3292, 2941, 2864, 2358, 2115, 1725, 1393, 1207, 1162, 1016, 961, 799, 754, 696. EI (MS) m/z (%): 150 (M⁺, 3), 149 (1.5), 135 (4), 121 (10), 107 (10), 93 (12), 84 (100), 79 (40), 77 (12), 67 (18), 55 (20), 54 (15), 53 (10), 51 (5), 41 (25), 39 (25). HRMS for C₁₀H₁₄O [M⁺]: calcd 150.1044, found 150.1045.

Diethyl-(6-oxospiro[4.4]non-1-yl)methylphosphonate 6a. According to the general procedure GP2, from 5a (116 mg, 0.77 mmol). FC (AcOEt) gave 6a (216 mg, 97%) as a 70:30 mixture of diastereomers.

1H NMR (300 MHz, CDCl₃) δ 4.18-3.96 (m, 8H), 2.58-2.41 (m, 1H), 2.41-1.45 (m, 29H), 1.41-1.21 (m, 12H). 31P NMR (300 MHz, CDCl₃) δ 31.84, 30.81. IR (cm⁻¹) film ν 2982, 2906, 2786, 1725, 1393, 1207, 1162, 1016, 961, 799, 754, 696. EI (MS) m/z (%): 288 (10), 260 (1), 231 (8), 191 (17), 152 (100), 125 (48), 79 (19), 55 (19), 41 (24). HRMS for C₁₄H₂₆O₄P [MH⁺]: calcd 289.1571, found 289.1568.
2-Oxo-1-pent-4-ynyl-cyclohexane carboxylic acid methyl ester. To a suspension of NaH (0.52 g, 12 mmol, 55-65% dispersion in mineral oil) in DMF (10 mL) was added dropwise at 0°C a solution of 2-oxo-cyclohexanecarboxylic acid methyl ester (1.56 g, 10 mmol) in DMF (10 mL). The cold bath was removed and the reaction mixture stirred at room temperature for 1.5 h. A solution of 5-iodo-pent-1-yne (1.94 g, 10 mmol) in DMF (10 mL) was added dropwise at room temperature and the reaction mixture was stirred for 12 h. The reaction was treated with 1N HCl. tert-BuOMe (20 mL) was added and the aqueous layer extracted with tert-BuOMe (4 x). The combined organic layers were washed with diluted HCl (1N), brine (2 x), dried over Na$_2$SO$_4$, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane/tert-BuOMe 80:20) to give the desired compound (1.73 g, 78%) as a pale yellow oil.

$^1$H NMR (300 MHz) δ 3.74 (s, 3H), 2.57-2.40 (m, 3H), 2.23-2.14 (m, 2H), 2.07-1.89 (m, 3H), 1.81-1.60 (m, 4H), 1.54-1.31 (m, 3H).

$^{13}$C NMR (100 MHz) δ 207.9, 172.6, 84.0, 68.8, 60.8 (C$_q$), 52.5, 41.2, 36.2, 34.0, 27.7, 23.7, 22.7, 18.9. IR (cm$^{-1}$) film ν 3288, 2946, 2865, 2361, 2115, 1708, 1434, 1309, 1309, 1209, 1132, 989, 816, 641. EI (MS) m/z (%): 223 (MH$^+$, 0.3), 207 (0.5), 191 (40), 179 (1.5), 156 (100), 151 (5), 145 (10), 135 (44), 134 (30), 126 (13), 124 (80), 121 (20), 120 (28), 119 (30), 109 (10), 107 (25), 106 (20), 105 (21), 100 (5), 93 (60), 91 (40), 87 (15), 81 (50), 79 (55), 77 (15), 68 (25), 67 (26), 59 (10), 55 (15), 53 (5), 41 (20). HRMS for C$_{13}$H$_{18}$O$_3$ [M$^+$]: calcd 222.1255, found 222.1253.

2-Pent-ynyl-cyclohexanone 5b. To a solution of 2-oxo-1-pent-4-ynyl-cyclohexane carboxylic acid methyl ester (0.67 g, 3 mmol) in DMF (4 mL) was added LiI (2.00 g, 15 mmol). The reaction mixture was stirred at 150 °C for 1.5 h. After completion (GC analysis), the reaction mixture was cooled at room temperature and treated with 1N HCl. tert-BuOMe (20 mL) was added and the aqueous layer extracted with tert-BuOMe (4 x). The combined organic layers were washed with 1N HCl, brine (2 x), dried over Na$_2$SO$_4$, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane/tert-BuOMe 90:10) to give 5b (429 mg, 87%) as a pale yellow oil.

$^1$H NMR (400 MHz) δ 2.41-2.35 (m, 1H), 2.32-2.24 (m, 2H), 2.21-2.14 (2H), 2.14-1.97 (m, 2H), 1.93 (t, J = 2.6 Hz, 1H), 1.90-1.81 (m, 2H), 1.70-1.60 (m, 2H), 1.56-1.48 (m, 2H), 1.44-1.27 (m, 2H). $^{13}$C NMR (100 MHz) δ 213.2, 84.5, 68.5, 50.4 (CH), 42.2, 34.1, 28.8, 28.2, 26.3, 25.0, 18.7. IR (cm$^{-1}$) film ν 3291, 2932, 2860, 2362, 2115, 1704, 1448, 1311, 1129, 883, 626. EI (MS) m/z (%): 164 (M$^+$, 0.5), 149 (1.5), 146 (0.5), 136 (1), 135 (2.5), 131 (1.5), 121 (5), 107 (5), 105 (3), 98 (100), 93 (14), 91 (15), 83 (20), 79 (30), 77 (15), 70 (15), 67 (16), 65 (5), 55 (20), 53 (10), 51 (5), 41 (30), 39 (21). HRMS for C$_{11}$H$_{16}$O [M$^+$]: calcd 164.1251, found 164.1253.

Diethyl-(6-oxospiro[4.5]dec-1-yl)methylphosphonate 6b. According to the general procedure GP2, from 5b (153 mg, 1.00 mmol). Flash chromatography (AcOEt) gave 6b (232 mg, 77%) as a 53:47 mixture of diastereomers. Retention time of the diastereomers (major/minor) determined by GC/MS analysis: 32.80/32.15.

$^1$H NMR (300 MHz, CDCl$_3$) δ 4.20-4.00 (m, 8H), 2.85-2.65 (m, 1H), 2.50-1.38 (m, 33H), 1.34 (t, J = 7.2 Hz, 6H), 1.32 (t, J = 7.3 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H). $^{31}$P NMR (300 MHz) δ 32.69, 32.19. IR (cm$^{-1}$) film ν 2934, 1698, 1445, 1390, 1240, 1162, 1097, 1052, 1023, 953, 827. EI (MS) m/z (%): 302 (17), 274 (10), 192 (30), 152 (100), 125 (71), 108 (23), 79 (37), 67 (36), 55 (17), 41 (22). HRMS for C$_{15}$H$_{27}$O$_4$P [M$^+$]: calcd 302.1647, found 302.1646.
3-Isopropyl-pent-4-ynoic acid methyl ester. To a solution of 2-(1-isopropyl-prop-2-ynyl)-malonic acid dimethyl ester (21.3 g, 100 mmol) in DMF (200 mL) was added LiCl (21.0 g, 500 mmol) and water (3.6 mL, 200 mmol). The reaction mixture was stirred at 150 °C for 1.5 h. After completion (GC analysis), the reaction mixture was cooled at room temperature and treated with 1N HCl. tert-ButOMe (20 mL) was added and the aqueous layer extracted with tert-ButOMe (4 x). The combined organic layers were washed with 1N HCl, brine (2 x), dried over Na₂SO₄, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane/tert-ButOMe 90:10) to give the desired compound (13.11 g, 85%) as a pale yellow oil.

1H NMR (100 MHz) δ 3.67 (s, 3H), 2.81-2.74 (m, 1H), 2.53-2.38 (m, 2H), 2.05 (d, J = Hz, 1H), 1.77-1.66 (m, 2H), 0.98 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H). 13C NMR (75 MHz) δ 172.4, 84.2, 70.9, 51.8, 37.8, 34.8, 31.0, 20.9, 17.9. IR (cm⁻¹) film ν 3296, 2961, 2875, 1737, 1436, 1388, 1370, 1262, 1164, 990, 892.

3-Isopropyl-pent-4-yn-1-ol. To a suspension of LiAlH₄ (2.08 g, 55 mmol) in Et₂O (100 mL) was added over 1 h dropwise at –20 °C a solution of 3-isopropyl-pent-4-ynoic acid methyl ester (7.71 g, 50 mmol) in Et₂O (50 mL). The cold bath was removed and the reaction mixture was stirred for 4 h at room temperature. The mixture was cooled down to –78°C and water (5 mL) was carefully added dropwise, followed by NaOH (5 mL, 1N), and water (5 mL). The cold bath was removed and the reaction mixture stirred at room temperature until a white precipitate appeared. The organic layer was filtered over a short pad of Celite® and the precipitate extracted with tert-ButOMe (3 x 20 mL). The combined organic phases were dried over Na₂SO₄, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (pentane/tert-ButOMe 70:30) to give the desired compound (5.99 g, 95%) as a pale yellow oil.

1H NMR (400 MHz) δ 3.83-3.79 (m, 2H), 2.45-2.40 (m, 1H), 2.08 (d, J = 2.5 Hz, 1H), 1.86-1.76 (broad s, 1H), 1.76-1.60 (m, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H). 13C NMR (100 MHz) δ 85.7, 71.0, 61.5, 35.4, 35.3, 31.7, 21.0, 18.4. IR (cm⁻¹) film ν 3500-3100 (broad), 3307, 2960, 2872, 2111, 1738, 1465, 1369, 1220, 1044, 881.

3-(2-Iodo-ethyl)-4-methyl-pent-1-yne. To a stirred solution of Ph₃P (15.2 g, 58 mmol) in CH₂Cl₂ (200 mL) cooled with an ice-bath were added, in rapid succession, imidazole (3.95 g) and I₂ (14.7 g) in equimolar amounts, followed after 1 h by a solution of 3-isopropyl-pent-4-yn-1-ol (5.99 g, 47.5 mmol) in CH₂Cl₂ (50 mL). The mixture was stirred for 2.5 h, after which it was evaporated, and the residue subjected to flash chromatography (pentane) to give 3-(2-iodo-ethyl)-4-methyl-pent-1-yn (7.40 g, 66%). 1H NMR (300 MHz) δ 3.44-3.37 (m, 1H), 3.30-3.22 (m, 1H), 2.45-2.37 (m, 1H), 2.10 (d, J = 2.6 Hz, 1H), 1.95-1.88 (m, 2H), 1.77-1.66 (m, 1H), 1.00 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H). 13C NMR (75 MHz) δ 84.2, 71.5, 39.6, 36.4, 31.2, 21.0, 18.6, 4.9. IR (cm⁻¹) film ν 3295, 2959, 2928, 2871, 2108, 1465, 1387, 1368, 1231, 1180, 931, 633. EI (MS) m/z (%): 236 (M⁺, 10), 208 (14), 194 (25), 155 (14), 141 (5), 128 (10), 127 (11), 109 (15), 107 (5), 95 (5), 94 (8), 91 (10), 81 (55), 79 (35), 77 (15), 69 (14), 67 (100), 66 (35), 65 (40), 63 (10), 57 (21), 55 (21), 51 (10), 43 (80), 41 (52), 41 (55). HRMS for C₈H₁₃I [M⁺]: calcd 236.0062, found 236.0057.

1-(3-Isopropyl-pent-4-ynyl)-2-oxo-cyclohexanecarboxylic acid methyl ester. To a suspension of NaH (0.78 g, 18 mmol, 55-65% dispersion in mineral oil) in DMF (10 mL) was added dropwise at 0 °C a solution of 2-oxo-cyclohexanecarboxylic acid methyl ester (2.34 g, 15 mmol) in DMF (10 mL). The cold bath was removed and the reaction mixture stirred at room temperature for 1.5 h. A solution of 3-(2-iodo-ethyl)-4-methyl-pent-1-yn (4.25 g, 18 mmol) in DMF (10 mL) was added dropwise at room temperature and the reaction mixture was stirred for 58 h. The reaction was treated with 1N HCl. tert-ButOMe (30 mL) was added
and the aqueous layer extracted with tert-BuOMe (4 x). The combined organic layers were washed with 1N HCl, brine (2 x), dried over Na₂SO₄, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane/tert-BuOMe 90:10) to give the desired compound (2.10 g, 53%) as a mixture of diastereomers in a 50:50 ratio as a pale yellow oil. ¹H NMR (400 MHz) mixture of diastereoisomers δ 3.73 (s, 3H), 3.72 (s, 3H), 2.55-2.41 (m, 6H), 2.21-2.06 (m, 2H), 2.04-2.03 (m, 2H), 2.01-1.60 (m, 14H), 1.53-1.25 (m, 6H), 0.97 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz) δ 208.1, 207.9, 172.8, 172.7, 85.8, 85.7, 70.7, 70.6, 60.9 (2C), 52.4, 52.3, 41.2, 41.1, 39.2, 39.1, 36.3, 35.9, 33.0, 32.7, 31.2, 31.1, 27.7, 27.6, 27.5, 27.4, 22.7, 22.6, 21.2, 21.1, 18.5, 18.3. IR (cm⁻¹) film ν 3289, 3028, 2956, 2930, 2870, 1701, 1710, 1451, 1368, 1197, 815, 733, 623. EI (MS) m/z (%): 264 (M⁺, 0.2), 249 (1.2), 233 (1.7), 222 (4), 221 (19), 205 (12), 193 (10), 189 (18), 183 (16), 177 (13), 161 (40), 157 (46), 156 (100), 145 (15), 133 (45), 124 (97), 123 (50), 121 (34), 119 (30), 111 (20), 109 (21), 107 (31), 105 (37), 95 (34), 93 (60), 91 (66), 81 (70), 79 (65), 77 (40), 69 (31), 67 (67), 65 (35), 59 (30), 55 (71), 53 (46), 43 (61), 41 (100), 39 (39). HRMS for C₁₆H₂₉O₃ [M⁺]: calcld 264.1725, found 264.1731.

2-(3-Isopropyl-pent-4-ynyl)-cyclohexanone 5c. To a solution of 1-(3-isopropyl-pent-4-ynyl)-2-oxo-cyclohexanecarboxylic acid methyl ester (1.65 g, 7.00 mmol) in DMF (20 mL) was added water (0.3 mL, 14 mmol) and LiI (2.00 g, 15 mmol). The reaction mixture was stirred at 150 °C for 1.5 h. After completion (GC analysis), the reaction mixture was cooled at room temperature and treated with 1N HCl. tert-BuOMe (20mL) was added and the aqueous layer extracted with tert-BuOMe (x4). The combined organic layers were washed with 1N HCl, brine (2 x), dried over Na₂SO₄, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane/tert-BuOMe 90:10) to give 5c (1.08 g, 75%) as a pale yellow oil. ¹H NMR (400 MHz) mixture of diastereoisomers δ 2.41-2.16 (m, 8H), 2.15-1.95 (m, 8H), 1.88-1.63 (m, 8H), 1.47-1.26 (m, 8H), 0.97 (d, J = 6.7 Hz, 6H), 0.95 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H). ¹³C NMR (100 MHz) δ 213.5, 213.4, 213.3, 186.3, 186.2, 70.4 (2C), 50.9, 50.6, 42.2, 42.1, 39.0, 38.8, 34.3, 34.1, 31.4, 31.2, 30.6, 30.1, 28.3, 28.2, 28.0, 27.7, 25.1, 24.9, 21.2 (2C), 18.4, 18.3. IR (cm⁻¹) film ν 3289, 2930, 2870, 2692, 1706, 1448, 1367, 1310, 1226, 1127, 623. EI (MS) m/z (%): 264 (M⁺, 0.2), 191 (1.5), 177 (2), 173 (1.6), 163 (1.5), 145 (5), 135 (7), 125 (7), 119 (4), 108 (6), 107 (10), 99 (10), 98 (100), 93 (25), 91 (15), 83 (20), 81 (17), 79 (22), 77 (12), 70 (16), 67 (20), 65 (10), 55 (30), 53 (10), 43 (15), 41 (25), 39 (15). HRMS for C₁₄H₂₂O [M⁺]: calcld 206.1670, found 206.1672.

2-Isopropyl-6-oxo-spiro[4.5]dec-1-yl-methylphosphonic acid dimethyl ester 6c. According to the general procedure GP2, from 5c (206 mg, 1.00 mmol) . FC (AcOEt) gave 6c (202 mg, 64%) as a 79:21 mixture of diastereomers. Retention time of the diastereomers (major/minor) determined by GC/MS analysis: 34.61/34.81

Major isomer: ¹H NMR (300 MHz, CDCl₃) δ 3.63 (d, J = 10.7 Hz, 3H), 3.62 (d, J = 10.7 Hz, 3H), 2.46-1.24 (m, 19H), 0.85 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 10.7 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 214.1, 59.8, 52.1 (d, J = 6.8 Hz), 51.4 (d, J = 9.9 Hz), 45.4 (d, J = 4.3 Hz), 39.8, 37.9 (d, J = 16.1 Hz), 29.6, 29.3 (d, J = 3.1 Hz), 28.4, 25.6, 25.0 (d, J = 138.3 Hz), 23.1, 22.7, 22.5, 15.9. ³¹P NMR (300 MHz, CDCl₃) δ 35.31. IR (cm⁻¹) film ν 2951, 2868, 1698, 1450, 1367, 1244, 1182, 1131, 1025, 976, 906, 813, 718. EI (MS) m/z (%): 316 (M⁺, 4), 273 (5), 233 (5), 206 (10), 192 (5), 179 (10), 165 (10), 151 (15), 137 (20), 125 (25), 124 (80), 110 (20), 109 (10), 97 (30), 95 (20), 81 (35), 79 (30), 78 (25), 66 (100), 65 (85), 55 (10), 47 (55), 41 (15). HRMS for C₁₀H₁₉O₃P [M⁺]: calcld 316.1803, found 316.1808.