Supporting Information

Enantioselective Conjugate Addition of a Lithium Ester Enolate Catalyzed by Chiral Lithium Amides

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Materials and Methods

Tetrahydrofuran (THF), toluene and diethylether (ether) were dried from sodium/benzophenone. All reagents were of reagent grade and were used as such or distilled prior to use. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck 5735 Kieselgel silica gel coated aluminium plates (60 F254) using UV light as visualizing agent and 7 % ethanolic phosphomolybdic acid, aqueous KMnO₄ or ninhydrin solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040 - 0.063 mm) was used for flash chromatography. ¹H and ¹³C NMR spectra were recorded at room temperature at 300 MHz and 75 MHz respectively and calibrated using residual undeuterated solvent as an internal reference. The solvent was deuteriochloroform, unless otherwise noted, with a calibration at 7.26 ppm for ¹H spectra and 77.16 ppm for ¹³C spectra. Chemical shifts (δ) are given in parts per million (ppm) and the coupling constants (*J*) in hertz (Hz). The following abbreviations were used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, hp = heptuplet, m = multiplet, br = broad. IR spectra were recorded by transmission on a IRTF spectrometer. Optical rotations were recorded at 20 °C on a polarimeter using the sodium D line (589 nm) and [α]_D are given in units of 10⁻¹ deg cm⁻² g⁻¹. The mass spectra were obtained under electron impact conditions (EI) at 70 eV ionizing potential; *i*-butane (ⁱBuH) was used for chemical ionization (CI). Melting points (m.p.) are uncorrected and were measured using a microscope apparatus. Elemental analyses were performed with an analyser. The reference given at the end of each protocol sends back to the previous description of the same compound.

Synthesis and data of the starting materials

tert-Butylcinnamate. A solution of methylcinnamate (5 g, 31 mmol) in freshly distilled ether (30 mL) was added to a solution of *t*-BuOK (8.3 g, 74 mmol) in ether (120 mL) at 0°C under nitrogen. Then, the mixture was stirred at 20°C for 30 min and cold water was added until the complete dissolution of the white precipitate (MeOK). The organic layer was separated, dried (MgSO₄) and concentrated under reduce pressure. The residue was purified by distillation (bp 65°C / 1 mmHg) to afford the desired product (3.59 g, 57%) as a colorless oil. (Vasin, V. A.; Razin, V. V. *Synlett* **2001**, 5, 658-660)

¹H NMR: δ 1.54 (9H, s), 6.37 (1H, d, *J* = 16.0), 7.32-7.43 (3H, m), 7.45-7.55 (2H, m), 7.59 (1H, d, *J* = 16.0). ¹³C NMR: δ 28.3, 80.6, 120.3, 128.1, 128.9, 130.1, 134.8, 143.7, 166.5. IR (film, NaCl): 1707, 1636, 1577, 1495, 1474, 1449, 1391, 1367, 1328, 1284, 1255, 1207, 1150. EIMS *m/z* 204 (*M*⁺, 15), 189 (4), 148 (100), 147 (97), 131 (48), 103 (29), 77 (16), 57 (28). Anal. Calcd. For C₁₃H₁₆O₂: C 76.44, H 7.90, Found: C 76.56, H 7.89.

(*E*) 4-Methylpenten-2-oic acid. Isobutyraldehyde (2.3 mL, 25 mmol) was added to a solution of malonic acid (2.1 g, 20 mmol) in pyridine (5 mL) at 0°C and the mixture was heated 5h at 55°C then 2h at 110°C. After cooling, the pyridine was eliminated under reduce pressure and the residue was diluted in ether. A solution of 50% sulfuric acid (3 mL) was added at 0°C, and the resulting solution was extracted with ether (6 * 20 mL). The organic layers were combined, dried (MgSO₄) and concentrated under reduce pressure. The crude product was purified by distillation (bp 100°C / 20 mmHg) to give the desired product (0.81 g, 35%) as a colorless oil. (Shabtai, J.; Ney-Igner, E; Pines, H. *J. Org. Chem.* **1981**, 46, 3795-3802).

¹H NMR: δ 1.05 (6H, d, *J* = 6.8), 2.46 (1H, doc, *J* = 6.8, 1.5), 5.76 (1H, dd, *J* = 15.8, 1.5), 7.05 (1H, dd, *J* = 15.8, 6.8), 12.27 (1H, s br). ¹³C NMR: δ 21.2, 31.2, 118.2, 158.5, 173.0. IR (film, NaCl): 1715, 1651, 1466, 1418, 1386, 1366, 1341, 1284, 1215, 1174.

(*E*) tert-Butyl 4-methylpent-2-enoate. Thionyl chloride (9.6 mL, 132 mmol) was added to a solution of (*E*) 4-methylpent-2-enoic acid (7.5 g, 66 mmol) in freshly distilled CH₂Cl₂ (75 mL) and the mixture was stirred 2h at room temperature. The excess of SOCl₂ was evaporated under reduced pressure, then CH₂Cl₂ (20 mL) was added and the resulting mixture was evaporated again. This procedure was repeated twice for a complete elimination of SOCl₂. *tert*-Butanol (31.2 mL, 330 mmol) was dropwise added to a solution of the previously formed acid chloride in CH₂Cl₂ (20 mL). The mixture was stirred 3h at room temperature, quenched with saturated NH₄Cl and extracted with CH₂Cl₂ (3 * 20 mL). The organic layers were combined, washed with saturated NaHCO₃ then brine, dried (MgSO₄) and concentrated under reduce pressure. The crude product was purified by distillation (bp 70 °C / 20 mmHg) to give the desired product (6.88 g, 62%) as a colorless oil.

^1H NMR: δ 1.04 (6H, d, J = 6.8), 1.48 (9H, s), 2.43 (1H, ddhp, J = 6.8, 6.8, 1.5), 5.71 (1H, dd, J = 15.8, 1.5), 6.84 (1H, dd, J = 15.8, 6.8). ^{13}C NMR: δ 21.3, 28.2, 30.8, 80.0, 120.3, 154.2, 166.4. IR (film, NaCl): 1755, 1652, 1461, 1391, 1366, 1346, 1315, 1301, 1258, 1204, 1154. EIMS m/z 170 (M^+ , <1), 155 (3), 115 (79), 114 (72), 97 (100), 69 (22), 57 (96).

2,4-Dimethylpentan-3-yl iso-butyrate 4 (precursor of the lithium ester enolate **1**). A mixture of *iso*-butyric acid (9.3 mL, 100 mmol), 2, 4-dimethylpentan-3-ol (42.0 mL, 300 mmol) and *para*-toluenesulfonic acid monohydrate (0.190 g, 1 mmol) in toluene (20 mL) was stirred at reflux for 48h in a Dean-Stark apparatus. After cooling to room temperature, the medium was quenched with saturated NaHCO_3 . The organic layer was washed with brine, dried (MgSO_4) and concentrated under reduce pressure. The residue was purified by distillation (bp 80°C / 10 mmHg) to afford the desired product (8.95 g, 48%) as a colorless oil. (Kambara, T.; Tomioka, K. *J. Org. Chem.* **1999**, *64*, 9282-9285)

^1H NMR: δ 0.85 (2 * 3H, d, J = 6.8), 0.87 (2 * 3H, d, J = 6.8), 1.19 (6H, d, J = 6.8), 1.89 (2H, dhp, J = 6.8, 6.0), 2.58 (1H, hp, J = 6.8), 4.58 (1H, t, J = 6.0). ^{13}C NMR: δ 17.3, 19.4 and 19.6, 29.5, 34.6, 82.0, 177.1. IR (film, NaCl): 1734, 1469, 1387, 1369, 1337, 1259, 1194, 1160, 1131, 1097, 1068. EIMS m/z 186 (M^+ , <1), 143 (12), 114 (2), 98 (3), 71 (100), 57 (13). Anal. calcd for $\text{C}_{11}\text{H}_{22}\text{O}_2$: C 70.92, H 11.90; found: C 70.97, H 11.95.

Typical procedure for the enantioselective conjugate addition of lithium ester enolate to α,β -unsaturated esters in the presence of chiral 3APLi.

Under an argon atmosphere, *n*-BuLi (0.85 mmol, 2.5 M solution in hexanes) was added to a solution of **3AP** (0.85 mmol) in THF (5 mL) at -20°C . After stirring 20 min, a solution of 2, 4-dimethylpentan-3-yl *iso*-butyrate **4** (0.65 mmol) in THF (4 mL) was added dropwise to the preformed solution of 3APLi and the resulting mixture was stirred 30 min at -20°C . *n*-BuLi (0.65 mmol, 2.5 M solution in hexanes) was added at -20°C and the mixture was aged 30 min at -78°C . A solution of α,β -unsaturated ester (0.5 mmol) in THF (1 mL) was added at -78°C and the mixture was stirred at -78°C for the indicated time. The reaction was quenched with saturated NH_4Cl and 3M HCl (2 mL) and was extracted with ether (3 * 15 mL) after reaching room temperature. The combined organic layers were washed with NaHCO_3 (15 mL) and brine (15 mL), dried (MgSO_4) and concentrated under reduce pressure. The residue was purified by silica gel column chromatography to give the corresponding Michael adducts.

5-*Tert*-butyl 1-(2,4-dimethylpentan-3-yl) 2,2,3-trimethylpentanedioate 7.

α,β -Unsaturated ester was (*E*) *tert*-butyl crotonate. Purification by flash chromatography on silica gel (cyclohexane/ether 95:5) gave **7** as a colorless oil.

^1H NMR: δ 0.81 (2 * 3H, d, J = 6.8), 0.83 (2 * 3H, d, J = 6.8), 0.87 (3H, d, J = 6.8), 1.07 (3H, s), 1.09 (3H, s), 1.38 (9H, s), 1.86 (2H, dhp, J = 6.8, 6.0), 1.91 (1H, dd, J = 14.9, 10.6), 2.30 (1H, dd, J = 14.9, 10.6), 2.33 (1H, ddq, J = 10.6, 6.8, 3.0), 4.55 (1H, t, J = 6.0). ^{13}C NMR: δ 15.0, 17.4 and 17.5, 19.9, 21.9, 22.7, 28.1, 29.6 and 29.7, 36.7, 38.9, 46.1, 80.2, 82.6, 172.5, 177.4. IR (film, NaCl): 1716, 1471, 1391, 1368, 1305, 1263, 1158, 1142, 1126, 1097 cm^{-1} . EIMS m/z 328 (M^+ , <1), 273 (2), 213 (7), 186 (8), 174 (5), 157 (100), 129 (63), 115 (5), 111 (22), 99 (14), 88, (18), 70 (27), 57 (81). Anal. calcd for $\text{C}_{19}\text{H}_{36}\text{O}_4$: C 69.47, H 11.05; found: C 69.59, H 10.98. $[\alpha]_{\text{D}}^{20} + 4.40$ (c 1.64, CHCl_3) when 76% ee.

HPLC 76% ee (Daicel Chiralpak AD-H, hexane/*i*-Pr 1000:1, 0.5 mL/min, 230 nm, major 16.4 min and minor 18.6 min)

5-*Tert*-butyl 1-(2,4-dimethylpentan-3-yl) 2,2-dimethyl-3-phenylpentanedioate 8.

α,β -Unsaturated ester was (*E*) *tert*-butyl cinnamate. Purification by flash chromatography on silica gel (cyclohexane/ether 95:5) gave **8** as a white solid.

m.p. = 82°C (cyclohexane).

^1H NMR: δ 0.82-0.95 (12H, d, J = 6.4), 1.09 (3H, s), 1.16 (9H, s), 1.18, (3H, s), 1.94 (2H, dhp, J = 6.4, 6.0), 2.61 (1H, dd, J = 15.1, 3.8), 2.79 (1H, dd, J = 15.1, 12.4), 3.62 (1H, dd, J = 12.4, 3.8), 4.65 (1H, t, J = 6.0), 7.15-7.35 (5H, m). ^{13}C NMR: δ 17.4 and 17.6, 19.8 and 19.9, 20.4, 25.9, 27.7, 29.5 and 29.7, 37.5, 46.2, 48.7, 80.2, 82.9, 126.9, 127.8, 130.2, 139.2, 171.2, 177.2. IR (film, NaCl): 1716, 1602, 1494, 1470, 1454, 1390, 1367, 1345, 1303, 1255, 1216, 1150. EIMS m/z 391 (M^+ , <1), 334 (15), 275 (4), 236 (32), 219 (94), 190 (31), 149 (85), 131 (19), 117 (10), 107 (33), 99 (21), 88, (55), 70 (16), 57 (100). Anal. calcd for $\text{C}_{24}\text{H}_{38}\text{O}_4$: C 73.81, H 9.81; found: C 73.79, H 9.73.

$[\alpha]_{\text{D}}^{20}$ -7.30 (c 0.65, CHCl_3) when 50 % ee.

HPLC 50% ee (Daicel Chiralpak AD-H, hexane/*i*-Pr 500:1, 0.5 mL/min, 254 nm, major 25.5 min and minor 44.9 min)

5-*Tert*-butyl 1-(2,4-dimethylpentan-3-yl) 3-*iso*-propyl-2,2-dimethylpentanedioate 9.

α,β -Unsaturated ester was (*E*) *tert*-butyl 4-methylpent-2-enoate. Purification by flash chromatography on silica gel (cyclohexane/ether 95:5) gave **9** as a colorless oil.

¹H NMR: δ 0.82 (3H, d, *J* = 6.8), 0.83-0.89 (4 * 3H, d, *J* = 6.8), 0.92 (3H, d, *J* = 6.8), 1.13 (3H, s), 1.14, (3H, s), 1.41 (9H, s), 1.78 (1H, dhp, *J* = 6.8, 1.9), 1.88 (2H, dhp, *J* = 6.8, 6.0), 2.13 (1H, dd, *J* = 16.2, 6.0), 2.19 (1H, dd, *J* = 16.2, 6.0), 2.39 (1H, dt, *J* = 6.0, 1.9), 4.57 (1H, t, *J* = 6.0). ¹³C NMR: δ 17.4 and 17.7, 18.6, 19.8 and 19.9, 22.0, 24.6, 25.3, 28.1, 28.9, 29.7 and 29.8, 32.5, 46.1, 48.0, 80.1, 82.8, 173.7, 177.8. IR (film, NaCl): 1728, 1724, 1529, 1471, 1422, 1390, 1367, 1335, 1303, 1250, 1154, 1098. EIMS *m/z* 357 (*M*⁺, <1), 241 (4), 202 (10), 185 (81), 169 (1), 157 (87), 139 (16), 115 (29), 99 (40), 88, (71), 70 (17), 57 (100). Anal. calcd for C₂₁H₄₀O₄: C 70.74, H 11.31; found: C 70.72, H 11.30.

$[\alpha]_D^{20}$: +1.1 (*c* 0.58, CHCl₃) when 15% ee.

HPLC 15% ee (Daicel Chiralpak AD-H, hexane/*i*-PrOH 500:1, 0.3 mL/min, 230 nm, major 23.5 min and minor 26.9 min)

Protocol A for the conjugate addition of the lithium enolate of 2, 4-dimethylpentan-3-yl *iso*-butyrate on *tert*-butyl crotonate in the presence of amide and amine. Under argon atmosphere, *n*-BuLi (0.65 mmol, 2.5 M solution in hexanes) was added to a solution of the first amine (0.65 mmol) in THF (5 mL) at -20°C. After stirring 20 min, a solution of 2,4-dimethylpentan-3-yl *iso*-butyrate (0.65 mmol) in THF (4 mL) was added dropwise to the resulting amide and the mixture was stirred 30 min at -20°C. *n*-BuLi (0.65 mmol, 2.5 M solution in hexanes) was added at -20°C and the mixture was aged 30 min at -78°C. Then, a solution of the other amine (0.65 mmol) in THF (2 mL) was added at -78°C and the mixture was aged for another 30 min at -78°C. A solution of *tert*-butyl crotonate (0.5 mmol) in THF (1 mL) was added at -78°C and the mixture was stirred at -78°C for 1h. The reaction was quenched with saturated NH₄Cl and 3M HCl (2 mL) and was extracted with ether (3 * 15 mL) after reaching room temperature. The combined organic layers were washed with NaHCO₃ (15 mL) and brine (15 mL), dried (MgSO₄) and concentrated under reduce pressure. The residue was purified by silica gel column chromatography (cyclohexane/ether 95:5) to give the corresponding Michael adduct **7**.

Protocol B for the conjugate addition of the lithium enolate of , 4-dimethylpentan-3-yl *iso*-butyrate on *tert*-butyl crotonate in the presence of amide and amine. Under argon atmosphere, *n*-BuLi (0.65 mmol, 2.5 M solution in hexanes) was added to a solution of amine (0.65 mmol) in THF (5 mL) at -20°C. After stirring for 20 min, a solution of 2,4-dimethylpentan-3-yl *iso*-butyrate (0.65 mmol) in THF (4 mL) was added dropwise to the resulting amide and the mixture was stirred 30 min at -20°C. Then, a solution of the other lithium amine (0.65 mmol) in THF (2 mL) was added at -20°C and the mixture was aged for 30 min at -78°C. A solution of *tert*-butylcrotonate (0.5 mmol) in THF (1 mL) was added at -78°C and the mixture was stirred at -78°C for 1h. The reaction was quenched with saturated NH₄Cl and 3M HCl (2 mL) and was extracted with ether (3 * 15 mL) after reaching room temperature. The combined organic layers were washed with NaHCO₃ (15 mL) and brine (15 mL), dried (MgSO₄) and concentrated under reduce pressure. The residue was purified by silica gel column chromatography (cyclohexane/ether 95:5) to give the corresponding Michael adduct **7**.

^1H and ^{13}C NMR spectra for (*E*) *tert*-butyl 4-methylpent-2-enoate

^1H NMR (CDCl_3 , 300 MHz)

^{13}C NMR (CDCl_3 , 75 MHz)

¹H and ¹³C NMR spectra for 7, 8 and 9

5-*Tert*-butyl 1-(2,4-dimethylpentan-3-yl) 2,2,3-trimethylpentanedioate 7

¹H NMR (CDCl₃, 300 MHz)

¹³C NMR (CDCl₃, 75 MHz).

5-*Tert*-butyl 1-(2,4-dimethylpentan-3-yl) 2,2-dimethyl-3-phenylpentanedioate 8

^1H NMR (CDCl_3 , 300 MHz)

^{13}C NMR (CDCl_3 , 75 MHz).

5-*Tert*-butyl 1-(2,4-dimethylpentan-3-yl) 3-*iso*-propyl-2,2-dimethylpentanedioate 9

^1H NMR (CDCl_3 , 300 MHz)

^{13}C NMR (CDCl_3 , 75 MHz).