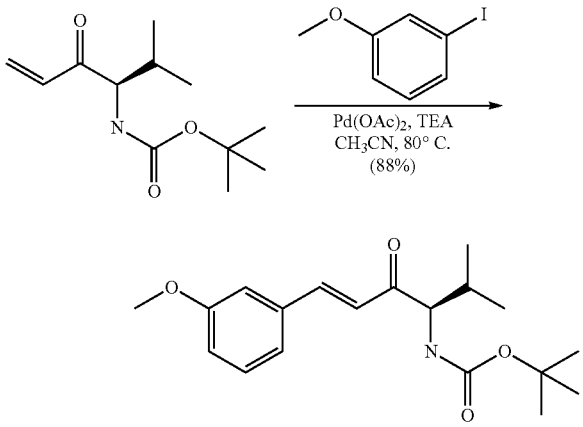
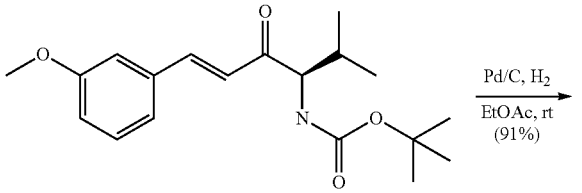


[(R)-(E)-1-Isopropyl-4-(3-methoxy-phenyl)-2-oxo-but-3-enyl]-carbamic acid tert-butyl ester

[0523] To a solution of ((R)-1-Isopropyl-2-oxo-but-3-enyl)-carbamic acid tert-butyl ester (13.54 g, 59.6 mmol) in dry acetonitrile (150 mL) under argon, was added 3-iodoanisole (13.96 g, 59.6 mmol), triethylamine (9.1 mL, 65.6 mmol) followed by palladium (II) acetate (335 mg, 1.49 mmol). The resulting clear yellow solution was heated to 80° C. Upon heating, the reaction darkened and the precipitation of palladium black occurred. After 15 h, the reaction mixture was allowed to cool to room temperature, quenched with water (150 mL) and diluted with ether (150 mL). The ether layer was washed with brine (100 mL) and the combined aqueous layers were extracted with ether (two 50 mL portions). The extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was immediately purified by silica gel chromatography (9:1 hexanes/EtOAc) to provide 17.6 g (88%) of [(R)-(E)-1-Isopropyl-4-(3-methoxy-phenyl)-2-oxo-but-3-enyl]-carbamic acid tert-butyl ester as a yellow oil. MS (ES+) m/e 334.0 $[M+H]^+$.

[(R)—(Z)-4-(3-Cyano-phenyl)-1-isopropyl-2-oxo-but-3-enyl]-carbamic acid tert-butyl ester

[0524] Following the procedure described for [(R)-(E)-1-isopropyl-4-(3-methoxy-phenyl)-2-oxo-but-3-enyl]-carbamic acid tert-butyl ester with 3-iodobenzonitrile (5.50 g, 24.0 mmol, 1 equiv) afforded the title compound as a yellow solid (7.4 g of ~90% purity material). ESMS $[M+H]^+$: 329.2.



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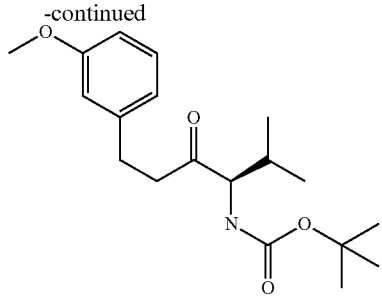
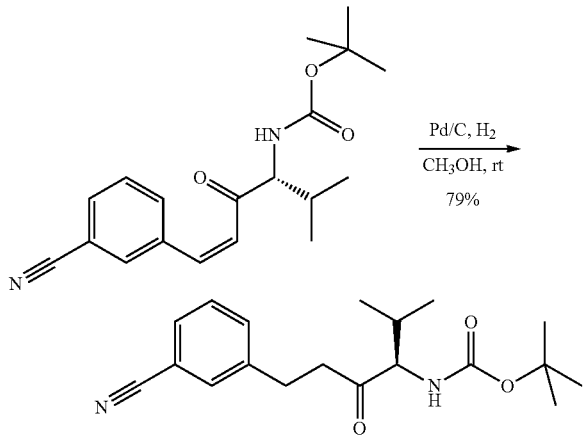


[(R)-(E)-1-Isopropyl-4-(3-methoxy-phenyl)-2-oxo-butyl]-carbamic acid tert-butyl ester

[0525] To a solution of [(R)-(E)-1-Isopropyl-4-(3-methoxy-phenyl)-2-oxo-but-3-enyl]-carbamic acid tert-butyl ester (17.6 g, 52.9 mmol) in ethyl acetate (450 mL) under nitrogen was added 10 wt % palladium on carbon (300 mg). The nitrogen was replaced with a balloon of hydrogen and the flask was purged. After 3 h, the reaction flask was purged with nitrogen and filtered through a pad of celite (rinsing with ethyl acetate). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (9:1 hexanes/EtOAc) to provide 16.2 g (91%) of [(R)-(E)-1-Isopropyl-4-(3-methoxy-phenyl)-2-oxo-butyl]-carbamic acid tert-butyl ester as a colorless oil. MS (ES+) m/e 336.4 $[M+H]^+$. $[\alpha]_D^{20}$=+19.1 (c=0.755, MeOH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (m, 1H), 6.80-6.77 (m, 2H), 6.75 (s, 1H), 5.13 (d, J=8.4 Hz, 1H), 4.28 (dd, J=8.8, 4.4 Hz, 1H), 3.81 (s, 3H), 2.93-2.88 (m, 2H), 2.85-2.76 (m, 2H), 2.14 (m, 1H), 1.46 (s, 9H), 1.00 (d, J=6.8 Hz, 3H), 0.75 (d, J=6.8 Hz, 3H).



[(R)-4-(3-Cyano-phenyl)-1-isopropyl-2-oxo-butyl]-carbamic acid tert-butyl ester

[0526] Palladium on carbon (740 mg of 10% wt/wt Pd/C) was added to a degassed solution of [(R)—(Z)-4-(3-cyano-phenyl)-1-isopropyl-2-oxo-but-3-enyl]-carbamic acid tert-butyl ester (7.4 g, 22.5 mmol, 1 equiv) in methanol (200 mL) at room temperature. The reaction mixture was thoroughly degassed and backfilled with hydrogen gas from a balloon. Hydrogenation proceeded at atmospheric pressure for 2.5 h.