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Highly Diastereoselective Prins-Type Cyclization of Cyclopropylvinylic Aldehydes Mediated by $TiCl_4$

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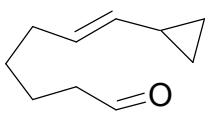
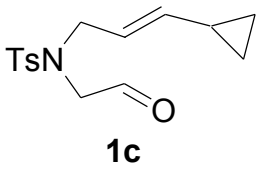
General: All reactions were run in flame dried glassware under an atmosphere of nitrogen. Diethyl ether (Et_2O) was dried by refluxing over sodium/benzophenone ketyl until a permanent purple coloration was presented, and distilled prior to use. Tetrahydrofuran (THF) was distilled from sodium-benzophenone under N_2. Dichloromethane (CH_2Cl_2) was distilled from CaH_2 prior to use. All liquid reagents purchased from the Aldrich were distilled properly prior to use, unless otherwise indicated. Purification was conducted by flash column chromatography on silica gel (230-400 mesh), eluting with a mixture of hexane and ethyl acetate, unless otherwise stated. Silica gel 60 (TA792685, 230-400 mesh) from Merck was used for column chromatography. All reactions were monitored by thin layer chromatography carried out on Merck silica gel plate (60 F_{254}) using UV light as visualizing agent and ethanolic anisaldehyde solution and heat as developing agent. The reported yields refer to isolated products. FT-IR spectra were recorded on a Nicolet 320. ^1H NMR spectra were recorded on a Varian Unity Inova at 500 MHz in $CDCl_3$ as a solvent with TMS or residual chloroform as the internal standard. ^{13}C NMR spectra were measured on a Varian Unity Inova at 125 MHz in $CDCl_3$ as a solvent.



1a

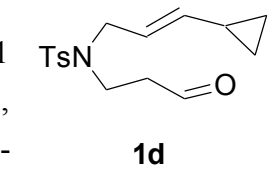
7-Cyclopropyl-hept-6-enal (1a): A colorless oil, TLC, R_f 0.41 (10:1 hexane/EtOAc); IR (neat) 3079, 3005, 2858, 1725, 1454, 1417, 1089, 940, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.30 (m, 3H, CH_2-C*H*$_2$-CH), 0.70 (m, 2H, CH_2-C*H*$_2$-CH), 0.87 (m, 3H, CH_2-C*H*$_2$-CH), 1.34 (m, 4H, CH_2-C*H*$_2$-CH_2), 1.46 (m, 4H, CH_2-C*H*$_2$-CH_2), 1.67 (m, 3H, CH_2-C*H*$_2$-CH_2), 1.99 (m, 1H, CH_2-C*H*$_2$-CH), 2.18 (m, 2H, CH_2-C*H*$_2$-CH=CH), 2.43 (m, 3H, CH_2-C*H*$_2$-CHO), 4.74 (m, 1H, CH_2-C*H*=CH), 5.29 (m, 1H, CH=C*H*-CH), 9.75 (m, 1H, CH_2-C*H*O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.8, 7.2, 10.0, 13.9, 21.9, 27.6, 29.5, 32.5, 44.2, 127.7, 134.8, 203.1; HRMS calcd for $C_{10}H_{16}O$: 152.1201. found: 152.1209

***N*-(3-Cyclopropyl-allyl)-4-methyl-*N*-(2-oxo-ethyl) benzenesulfonamide (1c):** A colorless oil, TLC, R_f 0.57 (1:1 hexane/EtOAc); IR (neat) 3083, 3005, 2925, 1733, 16665, 1598, 1450, 1342, 815 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.31 (m, 2H, CH_2-CH_2-CH), 0.70 (m, 2H, CH_2-CH_2-CH) 1.33 (m, 1H, CH_2-CH-CH_2), 2.44 (s, 3H, CH_3-C$(CH)_2$), 3.73 (dd, 2H, J = 7.0, 1.0 Hz, TsN-CH_2-CH), 3.75 (d, 2H, J = 1.4 Hz TsN-CH_2-CHO), 5.07 (ddt, 1H, J = 15.5, 9.0, 1.0 Hz, CH=CH-CH), 5.33 (dt, 1H, J = 15.5, 7.0 Hz, CH_2-CH=CH), 7.33 (d, 2H, J = 7.9 Hz, 2(C-CH=CH)), 7.69 (d, 2H, J = 7.9 Hz, 2(CH=CH-CSO_2)), 9.58 (d, 1H, J = 1.4 Hz, CH_2-CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.1, 13.6, 21.8, 51.9, 53.7, 56.0, 120.7, 127.7, 130.2, 135.2, 142.3, 144.2, 199.0; HRMS calcd for $C_{15}H_{19}NO_3S$: 293.1086. found: 293.1077.



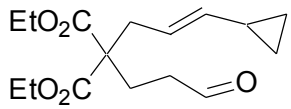
1c

***N*-(3-Cyclopropyl-allyl)-4-methyl-*N*-(3-oxo-propyl)-benzenesulfonamide (1d):** A colorless oil, TLC, R_f 0.33 (2:1 hexane/EtOAc); IR (neat) 3058, 2999, 2925, 1723, 1664, 1450, 1339, 1158, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.31 (m, 2H, CH_2-CH_2-CH), 0.69 (m, 2H, CH_2-CH_2-CH), 1.31 (m, 1H, CH_2-CH-CH_2) 2.43 (s, 3H, CH_3-C$(CH)_2$), 2.79 (td, 2H, J = 7.0, 1.1 Hz, CH_2-CH_2-CHO), 3.40 (t, 2H, J = 7.0 Hz, TsN-CH_2-CH_2) 3.72 (dd, 2H, J = 6.8, 1.1 Hz, TsN-CH_2-CH), 5.10 (ddt, 1H, J = 15.5, 8.7, 1.1 Hz, CH=CH-CH) 5.28 (dt, 1H, J = 15.5, 6.8, 1.1 Hz, CH_2-CH=CH), 7.31 (d, 2H, J = 7.9 Hz, 2(C-CH=CH)), 7.68 (d, 2H, J = 7.9 Hz, 2(CH=CH-CSO_2)), 9.76 (d, 1H, J = 1.1 Hz, CH_2-CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.2, 13.7, 21.9, 41.0, 44.3, 51.3, 121.8, 127.7, 130.2, 140.5, 143.9, 200.9; HRMS calcd for $C_{16}H_{21}O_3$: 307.1242. found: 307.1242.



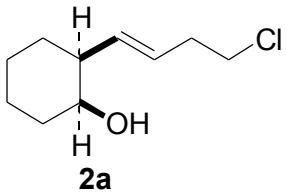
1d

2-(3-Cyclopropyl-allyl)-2-(3-oxo-propyl)-malonic acid diethyl ester (1e): A colorless oil, TLC, R_f 0.21 (5:1 hexane/EtOAc); IR (neat) 3081, 2983, 1728, 1446, 1368, 1265, 1193, 137 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.30 (m, 2H, CH_2-CH_2-CH), 0.67 (m, 2H, CH_2-CH_2-CH), 1.26 (t, 6H, J = 7.3 Hz, 2(CH_3-CH_2-CO_2)), 1.33 (m, 1H, CH_2-CH-CH_2) 2.18 (t, 2H, J = 7.8 Hz, C-CH_2-CH_2), 2.47 (td, 2H, J = 7.8, 1.2 Hz, CH_2-CH_2-CHO) 2.57 (dd, 2H, J = 7.6, 1.0 Hz, , C-CH_2-CH), 2.18 (q, 4H, J = 7.3 Hz, 2(CH_3-CH_2-CO_2)), 5.04 (ddt, 1H, J = 15.1, 8.5, 1.0 Hz, CH=CH-CH) 5.32 (dt, 1H, J = 15.1, 7.6 Hz, CH_2-CH=CH), 9.74 (d, 1H, J = 1.2 Hz, CH_2-CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.8, 13.8, 14.3, 36.9, 39.4, 57.1, 61.5, 120.8, 139.3, 171.1, 201.1; HRMS calcd for $C_{16}H_{24}O_5$: 296.1624. found: 296.1643.



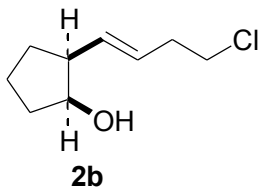
1e

General Procedure for Cyclisation



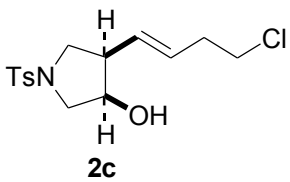
2a

2-(4-Chloro-but-1-enyl)-cyclohexanol (2a): A flame-dried Schlenk flask containing of 7-cyclopropyl-hept-6-enal (**1a**, 100 mg, 0.66 mmol) was evacuated and carefully purged with nitrogen three times and then charged with dry CH_2Cl_2 (3 mL), and then the solution was cooled to −78 °C. To a stirred solution at −78 °C was added $TiCl_4$ (80 μL, 0.72 mmol) in CH_2Cl_2 (0.5 mL) with gas-tight syringe via a syringe pump over 10 min along the wall of the flask while keeping the temperature at −78 °C. The resulting solution was allowed to stir at −78 °C for 2 h, and then warmed to 0 °C. The reaction was quenched by addition of aqueous $NaHCO_3$ (3 mL), and then the aqueous layer was extracted with CH_2Cl_2 (3 x 15). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography to give **2a** (92 mg, 0.49 mmol, 74%) as a colorless oil: TLC, R_f 0.36 (2:1 hexane/EtOAc); IR (neat) 3440, 3047, 2931, 1446, 1266, 1061, 973. 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.31 (m, 1H, CH_2-C*H*$_2$-CH_2), 1.41 (m, 1H, CH_2-C*H*$_2$-CH_2), 1.47-1.77 (m, 6H, CH_2-C*H*$_2$-C*H*$_2$-C*H*$_2$-CH), 2.27 (ddd, 1H, *J* = 13.2, 3.9, 2.8 Hz, CH-C*H*-CH_2), 2.51 (td, 2H, *J* = 13.5, 6.8 Hz, CH-C*H*$_2$-CH_2Cl), 3.56 (t, 2H, *J* = 6.8 Hz, CH_2-C*H*$_2$-Cl), 3.82 (ddd, 1H, *J* = 5.6, 2.8, 2.8 Hz, CH_2-C*H*-OH), 5.50 (ddt, 1H, *J* = 15.5, 6.8, 1.4 Hz, CH-C*H*=CH), 5.68 (ddt, 1H, *J* = 15.5, 6.8, 1.1 Hz, $_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 24.5, 26.6, 32.5, 36.3, 44.8, 70.0, 127.9, 135.3; HRMS calcd for $C_{10}H_{17}ClO$: 188.0968. found: 188.0976.



2b

2-(4-Chloro-but-1-enyl)-cyclopentanol (2b): A colorless oil, TLC, R_f 0.35 (2:1 hexane/EtOAc); IR (neat) 3382, 3049, 2957, 1447, 1266, 1086, 972, 738. cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 (m, 1H, CH_2-C*H*$_2$-CH_2), 1.56 (m, 1H, CH_2-C*H*$_2$-CH_2), 1.64 (m, 1H, CH_2-C*H*$_2$-CH) 1.74 (m, 1H, CH_2-C*H*$_2$-CH), 1.91 (m, 1H, CH_2-C*H*$_2$-CHOH), 1.98 (m, 1H, CH_2-C*H*$_2$-CHOH), 2.30 (m, 1H, CH_2-C*H*-CH), 2.48 (m, 2H, CH-C*H*$_2$-CH_2Cl) 3.53 (td, 2H, *J* = 7.0, 1.4 Hz, CH_2-C*H*$_2$-Cl), 3.84 (ddd, 1H, *J* = 7.0, 7.0, 7.0 Hz, CH_2-C*H*-OH), 5.49 (m, 2H, CH-C*H*=C*H*-CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 30.1, 33.7, 36.1, 44.6, 52.1, 78.7, 126.8, 135.9. HRMS calcd for $C_9H_{15}ClO$: 174.0811. found: 174.0813.

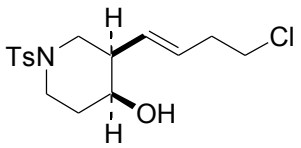


2c

4-(4-Chloro-but-1-enyl)-1-(toluene-4-sulfonyl)-pyrrolidin-3-ol (2c): A white solid, T TLC, R_f 0.32 (1:1 hexane/EtOAc); IR (neat): 3406, 3054, 2987, 1664, 1422, 1265, 1022, 896 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.41 (m, 2H, CH-C*H*$_2$-CH_2Cl), 2.45 (s, 3H, C*H*$_3$-C(CH)$_2$), 2.57 (ddd, 1H, *J* = 6.7, 6.7, 6.7 Hz, CH_2-*CH*-CH),

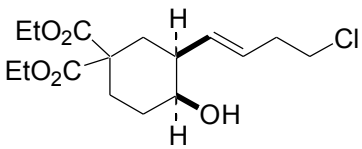
3.14 (m, 2H, TsN-CH_2-CH), 3.48 (t, 2H, J = 6.7 Hz, CH_2-CH_2-Cl), 3.56 (ddd, 2H, J = 10.5, 7.6, 15.2 Hz, TsN-CH_2-CHOH), 3.97 (m, 1H, CH_2-CH-OH), 5.24 (dddd, 1H, J = 15.2, 8.2, 1.8, 1.5 Hz, CH-CH=CH), 5.51 (dddd, 1H, J = 15.2, 7.6, 6.7, 0.6 Hz, CH=CH-CH_2), 7.34 (d, 2H, J = 7.9 Hz, 2(C-CH=CH)), 7.73 (d, 2H, 2H, J = 7.9 Hz, 2(CH=CH-CSO_2)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 49.1, 49.5, 51.3, 54.5, 73.1, 127.8, 128.0, 129.9, 130.0, 133.8, 143.9; HRMS calcd for $C_{15}H_{20}ClNO_3S$: 329.0852. found: 381.1796.

3-(4-Chloro-but-1-enyl)-1-(toluene-4-sulfonyl)-piperidin-4-ol (2d): A white solid, TLC, R_f 0.33 (1:1 hexane/EtOAc); IR (neat) 3397, 3054, 2987, 1643, 1421, 1265, 1020, 896 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.02 (m, 1H, CH_2-CH-CH), 2.23 (m, 1H, CH_2-CH_2-CHOH), 2.28 (m, 1H, CH_2-CH_2-CHOH), 2.43 (m, 2H, CH-CH_2-CH_2), 2.44 (s, 3H, CH_3-C$(CH)_2$), 2.48 (m, 1H, TsN-CH_2-CH_2), 2.53 (m, 1H, TsN-CH_2-CH_2), 3.23 (ddd, 1H, J = 4.1, 2.8, 2.8 Hz, CH_2-CH-OH), 3.56 (m, 2H, CH_2-CH_2-Cl), 3.69 (m, 2H, TsN-CH_2-CH), 3.76 (m, 1H, TsN-CH_2-CH), 5.28 (ddt, 1H, J = 15.5, 8.4, 1.2 Hz, CH-CH=CH), 5.67 (ddd, 1H, J = 15.5, 6.8, 6.8 Hz, CH=CH-CH_2), 7.33 (d, 2H, J = 8.0 Hz, 2(C-CH=CH)), 7.65 (d, 2H, J = 8.0 Hz, 2(CH=CH-CSO_2)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 32.2, 35.9, 44.1, 45.0, 48.0, 49.0, 71.0, 127.9, 130.0, 131.0, 131.7, 133.6, 143.9; HRMS calcd for $C_{16}H_{22}ClNO_3S$: 343.1009. found: 343.1007.



2d

3-(4-Chloro-but-1-enyl)-4-hydroxy-cyclohexane-1,1-dicarboxylic acid diethyl ester (2e): TLC, R_f 0.20 (2:1 hexane/EtOAc); IR (neat) 3438, 3053, 2985, 1725, 1444, 1422, 1265, 908, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (m, 6H, 2(CH_3-CH_2-CO_2)), 1.69 (m, 1H, CH_2-CH-CH), 1.92 (m, 1H, CH_2-CH_2-CH-OH), 2.00-2.18 (m, 4H), 2.38 (m, 1H, C-CH_2-CH), 2.53 (m, 2H, CH-CH_2-CH_2Cl), 3.57 (m, 2H, CH_2-CH_2-Cl), 3.88 (ddd, 1H, J = 5.1, 2.5, 2.5 Hz, CH_2-CH_2-OH), 4.21 (m, 4H, 2(CH_3-CH_2-CO_2), 5.55 (dddd, 1H, J = 15.7, 6.8, 6.8, 1.1 Hz, CH-CH=CH), 5.63 (ddt, 1H, J = 15.7, 5.6, 1.1 Hz, CH=CH-CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 24.5, 29.2, 36.1, 40.8, 44.5, 54.9, 61.4, 61.6, 67.5, 127.8, 135.0, 171.3, 172.2. HRMS calcd for $C_{16}H_{25}ClO_5$: 332.1391. found: 332.1381.



2e

Copies of ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) Spectra