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Tandem Prins cyclization for the Stereo selective synthesis of 3,6-dihydro-*2H*-pyran scaffolds

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ABSTRACT

A wide array of aldehydes undergo smooth cross-coupling with 3-methylene-5-phenylpent-4-yn-1-ol in the presence of 10 mol% $BF_3{\cdot}OEt_2$ at 0 °C in dichloromethane afforded the corresponding 6-phenyl-4-(phenylethynyl)-3,6-dihydro-2H-pyran derivatives in good yields with excellent stereoselectively. This is the first report for the synthesis of 6-phenyl-4-(phenylethynyl)-3,6-dihydro-2H-pyran scaffolds via Prins cyclization protocol.

Key words: 3-methylene-5-phenylpent-4-yn-1-ol, 10 mol% $BF_3{\cdot}OEt_2$, 6-phenyl-4-phenylethynyl)-3,6-dihydro-2H-pyran, Prins reactions.

INTRODUCTION

Substituted pyran motifs constitute the core structural unit in numerous biologically active natural products such as calixyn L,[1] ambruticin,[2] kendomycin[3] (Figure 1) and have diverse applications in cosmetics and agro chemicals as well.4 The dihydropyran skeleton of this family is distinctly important since functionalized dihydropyrans are versatile building blocks widely used in the synthesis of biologically active molecules[5] and this structural moiety exists in many natural products such as laulimalide[6] and aspergillide C (Figure 1).[7] The presence of double bond in cyclic system is not only responsible for their biological properties but also serve as a functional group for further manipulations in organic synthesis.[8] They can also be used as building blocks in organic synthesis.[9] There are different methods towards the construction of dihydropyrans including hetero-Diels-Alder reactions,[10] olefin metathesis,[11] base promoted cyclizations of sulfenyl dienols,[12] oxonium-ene reactions,[13] [4+2] annulations,14 intramolecular C-C bond formation of alkyne-epoxide,[15] and Prins cyclization reactions.]16]Among various methods available, Prins cyclization is considered to be the most elegant tool as it provides the desired product in a single step with high diastereoselectivity.

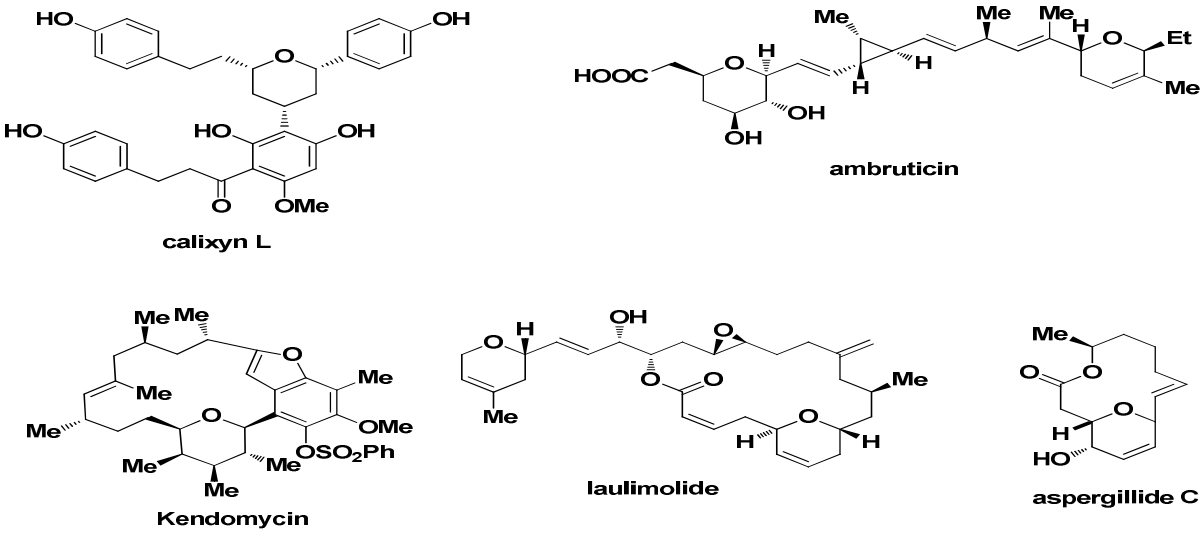
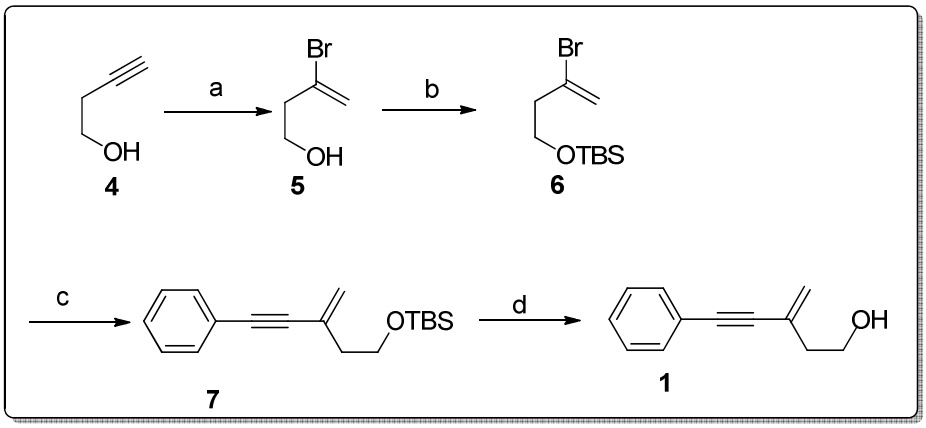


Figure1. Structure of natural products containing pyran ring

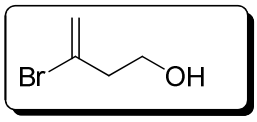
MATERIALS AND METHODS



Scheme 2. Synthetic procedure for 1

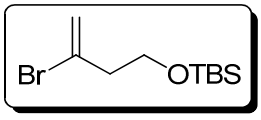
***Reagents & conditions**: (a) PBr_3, H_2O, TEAB, DCM, 40 °C (b) TBSCl, imidazole, DCM, 0 °C to rt (c) Phenyl acetylene, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, 60 °C, 12 hrs, (d) TBAF,THF.*

General Procedure for 3-bromobut-3-en-1-ol : 5



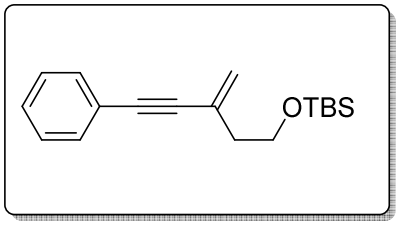
HBr gas was produced by adding PBr_3 (1.46 mL, 11 mmol) dropwise to water (0.59 mL, 33mmol). Thus produced HBr gas was bubbled through tetraethylammonium bromide (6.3 g) in 40 mL of dichloromethane at 0 °C, after which the weight of dichloromethane solution of TEAB. HBr was found to be 2.25g. To this solution, 3-butyn-1-ol **4** (1.89 mL, 12 mmol) was added and the resulting mixture was heated at 40 °C for 5 h. After completion, the mixture was cooled to 0 °C and diluted with water and then extracted with ether, dried over Na_2SO_4 and the solvent was removed in vacuum. The crude product **5** was used as such for further step.

General Procedure for (3-bromobut-3-enyloxy)(*tert*-butyl)dimethylsilane: 6



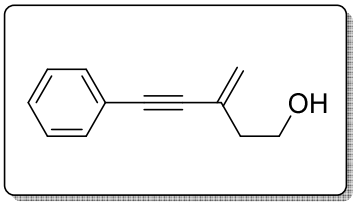
3-Bromobut-3-en-1-ol **2a** (5.0 g, 33.3 mmol) was taken in to dry DCM and imidazole (2.49 g, 36.6 mmol) was added at 0 °C. After few min, *tert*-butyldimethylsilyl chloride (5.0g, 33.3 mmol) was added and the mixture was stirred at room temperature for 30 min. The reaction was quenched with cold water and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was then purified by flash chromatography on silica gel column with hexane-ethyl acetate to give the compound **6** as a liquid.

General Procedure for tert-butyldimethyl((3-methylene-5-phenylpent-4-yn-1-yl)oxy)silane : 7



A solution of **(**3-bromobut-3-enyloxy)(*tert*-butyl)dimethylsilane **6** (750 mg, 5 mmol) and 1-alkyne (1.3 ml, 10 mmol) in NEt_3(10 ml) was added $Pd(PPh_3)_2Cl_2$ (70 mg, 2 mol%) and CuI (38 mg, 4 mol%) at room temperature under Argon. The resulting mixture was stirred at 60 °C for 12 h, cooled to room temperature, evaporated to dryness, diluted with EtOAc and washed with aq. NH_4Cl. The organic phase was separated, dried over Na_2SO_4, and evaporated to dryness under reduced pressure to give the crude compound **7**, which was purified by column chromatography.

General Procedure for 3-methylene-5-phenylpent-4-yn-1-ol : 1



To a solution of **7** (1.0 g, 4.3 mmol) in THF (15 mL) at 0 °C was added TBAF (1.0 N in THF, 4.3 mL, 4.3 mmol). After stirring for 10 min, the reaction mixture was quenched with sat. NH_4Cl solution and extracted thrice with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and then filtered and evaporated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc) to afford the required alcohol **1** (85%) as a viscous liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 – 7.41 (m, 2H), 7.35 – 7.28 (m, 3H), 5.55 (d, J = 1.8 Hz, 1H), 5.49 – 5.33 (m, 1H), 3.89 (t, J = 6.1 Hz, 2H), 2.59 – 2.46 (m, 2H)ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 131.63, 128.41, 128.04, 123.79, 122.92, 89.96, 88.93, 60.94, 40.58ppm **MS (ESI)**: *m/z* 173 $(M+H)^+$; **HRMS (ESI):** calcd for $C_{12}H_{13}O$: 173.0944 $(M+H)^+$,Found 173.0956.

Typical procedure for the Prins cyclization:
To a stirred solution of homoallylic diol **1** (0.5 mmol) and aldehyde (0.6 mmol) in dry dichloromethane (5 mL) was added 10 mol% $BF_3.OEt_2$ at 0 °C. The resulting mixture was stirred at the same temperature under nitrogen atmosphere for the specified time. After completion, as indicated by TLC, the reaction mixture was quenched with sat. $NaHCO_3$ solution (1.0 mL) and extracted with dichloromethane (2x5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuum. The resulting crude product was purified by silica gel column chromatography (60–120 mesh) using ethyl acetate/hexanes as eluent to afford the pure product.

Spectral data for the 3,6-dihydro-2H-pyran derivatives :
Characterization data of products:
4-(4-(phenylethynyl)-5,6-dihydro-2H-pyran-2-yl)benzonitrile:(3a)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 – 7.65 (m, 2H), 7.51 (d, J = 8.2 Hz, 2H), 7.42 (dt, J = 6.6, 3.6 Hz, 2H), 7.32 (dd, J = 3.8, 2.7 Hz, 3H), 6.32 – 6.19 (m, 1H), 4.73 – 4.58 (m, 1H), 4.53 – 4.38 (m, 2H), 2.53 – 2.41 (m, 2H)ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 147.04, 132.35, 131.90, 131.53, 128.37, 126.44, 123.29, 118.25, 111.61, 104.22,

89.09, 74.26, 66.12, 35.95 ppm; **IR (KBr)**: υ 2925,2228,1721,1642, 1214,756, 668cm^{-1}; **MS (ESI)**: *m/z* 286 (M+H)$^+$; **HRMS (ESI):** calcd for $C_{20}H_{15}NO$: 286.0144 (M+H)$^+$,Found 286.0156.

6-(4-nitrophenyl)-4-(phenylethynyl)-3,6-dihydro-2H-pyran: (3b)
^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.26 – 8.22 (m, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.45 – 7.40 (m, 2H), 7.35 – 7.29 (m, 3H), 6.34 – 6.19 (m, 1H), 4.77 – 4.63 (m, 1H), 4.63 – 4.34 (m, 2H), 2.57 – 2.41 (m, 2H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** *δ* 149.15, 147.29, 131.85, 131.53, 128.38, 126.51, 123.75, 118.21, 88.58, 74.30, 66.63, 36.43ppm; **IR (KBr)** : υ3019,2228, 1642, 1519, 1347,1214,747, 667cm^{-1}; **MS (ESI)**: *m/z* 306 (M+H)$^+$; **HRMS (ESI)**: calcd for $C_{19}H_{16}NO_3$: 306.0442 (M+H)$^+$,Found 306.0456.

6-(4-bromophenyl)-4-(phenylethynyl)-3,6-dihydro-2H-pyran: (3c)
^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.52 – 7.48 (m, 2H), 7.44 – 7.41 (m, 2H), 7.34 – 7.30 (m, 4H), 7.28 (t, *J* = 1.9 Hz, 1H), 6.25 (dt, *J* = 4.7, 1.8 Hz, 1H), 4.55 (dt, *J* = 21.5, 10.7 Hz, 1H), 4.50 – 4.41 (m, 2H), 2.49 (tdt, *J* = 14.1, 11.6, 6.5 Hz, 2H)ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** *δ* 140.77, 132.03, 131.57, 128.34, 127.61, 123.08, 121.53, 118.57, 88.84, 74.57, 66.48, 36.47ppm; **IR (KBr)**: υ 3019, 2923, 2852,1721,1672, 1594, 1531, 1488,1214, 1071,1010, 751, 667 cm^{-1}; **MS (ESI):** *m/z* 341 (M+H)$^+$; **HRMS (ESI):** calcd for $C_{19}H_{17}BrO$: 341.0342 (M+2H)$^+$,Found 341.0326.

4-(phenylethynyl)-1-oxaspiro[5.5]undec-4-ene: (3d)
^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.46 – 7.40 (m, 2H), 7.33 – 7.28 (m, 3H), 6.24 – 6.01 (m, 1H), 4.22 (q, *J* = 2.8 Hz, 2H), 2.17 (dd, *J* = 4.6, 2.7 Hz, 2H), 1.75 (dd, *J* = 12.9, 4.4 Hz, 2H), 1.66 – 1.59 (m, 2H), 1.48 (dq, *J* = 9.2, 5.1 Hz, 3H), 1.41 (ddd, *J* = 14.0, 7.3, 3.1 Hz, 2H), 1.36 – 1.31 (m, 1H)ppm; **^{13}C NMR (75 MHz, $CDCl_3$)**: *δ* 140.51, 131.95, 128.69, 128.07, 123.85, 117.34, 70.78, 60.46, 39.04, 34.65, 29.73, 25.95, 21.71ppm; **IR (KBr)** : υ 2925,2854,2202, 1707,1446, 1214, 1087,996,756,690, 667cm^{-1}; **MS (ESI):** *m/z* 253 (M+H)$^+$; **HRMS (ESI):** calcd for $C_{18}H_{21}O$: 253.0142 (M+H)$^+$,Found 253.0136.

6-octyl-4-(phenylethynyl)-3,6-dihydro-2H-pyran:(3e)
^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.50 – 7.42 (m, 2H), 7.38 – 7.30 (m, 3H), 4.09 – 3.97 (m, 1H), 3.82 – 3.68 (m, 1H), 3.46 (s, 2H), 2.13 – 2.01 (m, 2H), 1.84 – 1.63 (m, 2H), 1.51 – 1.34 (m, 5H), 0.94 – 0.81 (m, 8H)ppm; **^{13}C NMR (75 MHz, $CDCl_3$):** *δ* 131.52, 128.34, 88.64, 75.27, 73.32, 65.36, 50.91, 43.15, 37.88, 36.05, 31.65, 29.72, 25.53, 22.66, 14.09 ppm; **IR (KBr)**: υ 2956,2855,1621,1492, 1460, 1435, 1440, 1284, 1130, 656, 568cm^{-1}; **MS (ESI)**: *m/z* 283 (M+H)$^+$; **HRMS (ESI):** calcd for $C_{20}H_{27}O$: 283.0242 (M+H)$^+$,Found 283.0236.

6-(naphthalen-2-yl)-4-(phenylethynyl)-3,6-dihydro-2H-pyran: (3f)
^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.17 – 8.04 (m, 1H), 7.90 – 7.83 (m, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 7.1 Hz, 1H), 7.61 – 7.56 (m, 1H), 7.55 – 7.45 (m, 3H), 7.42 – 7.37 (m, 2H), 7.33 – 7.28 (m, 2H), 5.54 – 5.41 (m, 1H), 4.15 – 4.03 (m, 1H), 3.58 (s, 1H), 3.49 (s, 1H), 2.28 – 2.08 (m, 2H)ppm; **^{13}C NMR (101 MHz, $CDCl_3$):** *δ* 137.92, 137.31, 133.77, 132.04, 128.54, 125.48, 123.16, 122.51, 89.75, 88.32, 85.42, 74.57, 71.22, 66.07, 63.62, 51.54, 50.83, 44.26, 42.92, 38.01, 35.37, 29.75ppm; **IR (KBr)**: υ 3054, 2927,2855,1597,1489, 1443, 1340,1303, 1259, 1143,1122, 1080,1039, 798,776, 754,690,580cm^{-1}; **MS (ESI):** *m/z* 311 (M+H)$^+$; **HRMS (ESI):** calcd for $C_{23}H_{19}O$: 311.0240 (M+H)$^+$,Found 311.0236.

6-([1,1'-biphenyl]-4-yl)-4-(phenylethynyl)-3,6-dihydro-2H-pyran: (3g)
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.63 – 7.58 (m, 4H), 7.49 – 7.41 (m, 6H), 7.37 – 7.29 (m, 4H), 6.27 (dt, *J* = 3.4, 2.0 Hz, 1H), 4.64 (dd, *J* = 10.2, 3.5 Hz, 1H), 4.53 – 4.47 (m, 2H), 2.73 – 2.44 (m, 2H)ppm; **^{13}C NMR (101 MHz, $CDCl_3$):** *δ* 140.92, 140.71, 132.19, 131.55, 128.79, 128.35, 128.23, 127.27, 127.15, 126.41, 123.19, 118.74, 88.89, 75.18, 66.58, 36.32ppm; **IR (KBr)**: υ 3030, 2925, 2820,1597, 1487,1442,1370,1238,1215, 1128, 1099, 1023, 1007, 911,832,756,691,574cm^{-1}; **MS (ESI):** *m/z* 337 (M+H)$^+$; **HRMS (ESI):** calcd for $C_{25}H_{21}O$: 337.0140 (M+H)$^+$,Found 337.0136.

6-isobutyl-4-(phenylethynyl)-3,6-dihydro-2H-pyran: (3h)
^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.51 – 7.41 (m, 4H), 7.37 – 7.28 (m, 5H), 4.08 – 3.98 (m, 1H), 3.79 – 3.67 (m, 1H), 3.46 (s, 2H), 2.06 (ddt, *J* = 34.0, 28.7, 11.9 Hz, 2H), 1.42 (dd, *J* = 22.9, 11.5 Hz, 1H), 1.32 – 1.22 (m, 2H), 0.98 – 0.87 (m, 6H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$):** *δ* 131.75, 128.53, 122.35, 88.50, 73.48, 65.23, 50.62, 45.08, 43.49, 37.57, 31.46, 29.73, 24.52, 23.15, 22.45ppm; **IR (KBr)** : υ2958, 2924, 2853,2204, 1720,1605, 1490, 1461,1418, 1363,1272,1055,1011,828,756, 691cm^{-1}; **MS (ESI):** *m/z* 317 (M+H)$^+$; **HRMS (ESI):** calcd for $C_{23}H_{25}O$: 337.0230 (M+H)$^+$,Found 337.0126.

6-(4-isopropylphenyl)-4-(phenylethynyl)-3,6-dihydro-2H-pyran: (3i)
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.46 – 7.40 (m, 2H), 7.34 – 7.28 (m, 5H), 7.25 – 7.21 (m, 2H), 6.40 – 6.08 (m, 1H), 4.56 (dt, *J* = 11.3, 5.6 Hz, 1H), 4.51 – 4.40 (m, 2H), 2.92 (dq, *J* = 13.8, 6.8 Hz, 1H), 2.60 (ddt, *J* = 13.4, 5.9, 3.3 Hz,

1H), 2.46 (dd, *J* = 10.3, 7.6 Hz, 1H), 1.25 – 1.16 (m, 6H)ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** *δ* 148.51, 138.98, 132.21, 131.53, 128.33, 128.18, 126.55, 126.05, 123.22, 118.92, 88.81, 75.35, 66.48, 36.38, 33.90, 29.73, 24.10ppm; **IR(KBr)**: υ 2954,2925,2854,1726,1598,1490,1465,1380,1367,1304,1153,1093,1030,756, 691,641cm^{-1}; **MS (ESI):** *m/z* 303 $(M+H)^+$; **HRMS (ESI):** calcd for $C_{22}H_{23}O$: 303.0130 $(M+H)^+$,Found 303.0126.

6-butyl-4-(phenylethynyl)-3,6-dihydro-2H-pyran(3j)
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.46 – 7.36 (m, 2H), 7.29 (ddt, *J* = 6.4, 2.7, 2.2 Hz, 3H), 5.45 (dt, *J* = 18.3, 9.2 Hz, 1H), 3.88 – 3.73 (m, 2H), 2.58 (t, *J* = 6.5 Hz, 1H), 2.16 – 1.89 (m, 2H), 1.70 – 1.57 (m, 1H), 1.29 (d, *J* = 6.3 Hz, 2H), 1.25 (s, 1H), 0.95 – 0.84 (m, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** *δ* 131.46, 128.37, 123.08, 71.78, 70.03, 62.64, 61.86, 41.68, 38.12,29.73,18.51,14.12ppm;**IR (KBr)**: υ 2957,2926, 870,2200,1721,1598,1491,1443, 1266,1152, 1072, 982,811, 757, 691cm^{-1}; **MS (ESI):** *m/z* 227 $(M+H)^+$; **HRMS (ESI)**: calcd for $C_{16}H_{19}O$: 227.0133 $(M+H)^+$,Found 227.0136.

6-phenyl-4-(phenylethynyl)-3,6-dihydro-2H-pyran(3k):
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.48 – 7.40 (m, 2H), 7.40 – 7.33 (m, 3H), 7.32 – 7.27(m,3H), 7.27 – 7.24 (m, 1H), 7.23 – 7.09 (m, 1H), 6.36 – 6.12 (m, 1H), 4.58 (dt, *J* = 20.6, 10.3 Hz, 1H), 4.53 – 4.39 (m, 1H), 4.17 – 3.74 (m, 1H), 2.69 – 2.40 (m, 2H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** *δ* 141.69, 132.16, 131.54, 128.59, 128.34, 128.21, 127.86, 127.55, 125.95, 123.38, 118.77, 88.88, 75.52, 66.56, 36.40 ppm; **IR (KBr, neat)**: υ 2924, 2854, 1719,1456, 1450, 1250, 1214, 1125,1060, 756, 695 cm^{-1}; **MS (ESI):** *m/z* 261 $(M+H)^+$; **HRMS (ESI):** calcd for $C_{19}H_{17}O$: 261.0233 $(M+H)^+$,Found 261.0230.

2-(4-(phenylethynyl)-5,6-dihydro-2H-pyran-2-yl)benzonitrile (3l):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.42 (dd, *J* = 3.7, 1.6 Hz, 3H), 7.36 (d, *J* = 2.1 Hz, 1H), 7.33 – 7.29 (m, 3H), 7.13 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.17 (d, *J* = 1.5 Hz, 1H), 5.12 (s, 1H), 3.83 (t, *J* = 5.5 Hz, 2H), 2.25 – 2.17 (m, 2H)ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** *δ* 145.70, 143.39, 138.09, 132.92, 131.76, 128.31, 125.68, 124.48, 119.12, 114.32, 111.31, 110.78, 103.44, 96.29, 91.18, 75.10, 59.53, 31.46ppm; **IR (KBr, neat)**: υ 2922,2850,1721,1649,1536,1461,1263,1184,1080, 966, 772, 578 cm^{-1}; **MS (ESI):** *m/z* 286 $(M+H)^+$; **HRMS (ESI):** calcd for $C_{20}H_{15}NO$: 286.0244 $(M+H)^+$,Found 286.0246.

6-(4-chlorophenyl)-4-(phenylethynyl)-3,6-dihydro-2H-pyran (3m):
^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.53 (d, *J* = 8.6 Hz, 1H), 7.44 – 7.41 (m, 2H), 7.38 – 7.35 (m, 1H), 7.31 (dd, *J* = 5.0, 1.8 Hz, 3H), 7.26 (s, 1H), 7.13 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.29 – 6.20 (m, 1H), 4.57 (dd, *J* = 9.8, 3.8 Hz, 1H), 4.49 – 4.43 (m, 2H), 2.48 (ddt, *J* = 15.2, 11.5, 6.5 Hz, 2H)ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** *δ* 140.25, 133.42, 132.04, 131.53, 128.63, 128.35, 128.27, 127.29, 124.48, 124.04, 123.09, 119.12, 118.52, 88.84, 88.68, 74.83, 66.20, 36.34ppm; **IR (KBr, neat)**: υ 2922, 2852,2203,1721,1491,1214,1184,1089,823,755,667cm^{-1}; **MS (ESI)**: *m/z* 296 $(M+2H)^+$; **HRMS (ESI):** calcd for $C_{19}H_{16}ClO$: 296.0134 $(M+2H)^+$,Found 296.0136.

4-(phenylethynyl)-6-(p-tolyl)-3,6-dihydro-2H-pyran (3n):
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.50 (dddd, *J* = 5.9, 4.6, 4.0, 2.1 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.37 – 7.34 (m, 1H), 7.30 (ddd, *J* = 3.9, 3.4, 2.1 Hz, 2H), 7.23 (dd, *J* = 6.9, 4.3 Hz, 1H), 7.14 (dd, *J* = 10.7, 8.1 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 1H), 6.35 – 6.07 (m, 1H), 5.60 – 5.41 (m, 1H), 4.26 – 4.11 (m, 1H), 3.82 – 3.60 (m, 1H), 2.33 (d, *J* = 3.4 Hz, 3H), 2.16 – 2.04 (m, 2H)ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** *δ* 138.69, 137.43, 132.21, 131.54, 129.15, 128.33, 128.19,125.93,118.80,75.29,66.40,36.30,21.18ppm; **IR(KBr, neat)**: υ 3020,2958,2924,2859,2199,1720,1672,1490, 1443, 1214,753, 667cm^{-1}; **MS (ESI):** *m/z* 275 $(M+H)^+$; **HRMS (ESI)**: calcd for $C_{20}H_{19}O$: 275.0124 $(M+H)^+$,Found 275.0128.

RESULTS AND DISCUSSION

Inspired by the versatility of cascade reactions in organic synthesis,[17] we herein report a novel synthesis of 3,6-dihydro-2H-pyran scaffolds through a Prins reaction. The reaction proceeds in two steps but in one-pot through a sequential Prins . The Synthetic procedure for required enediol **1**was started from homopropargyl alcohol **4** which upon treatment Hydrobromination reaction by using PBr_3/H_2O gave the vinyl bromide product **5**, which was further protected as silyl ether by using TBSCl in DCM to afford **6**. Coupling reaction over **5** under Sonogashira protocol with Phenylacetylene, followed by deprotection of silylether *i.e.* TBS removal under treatment with TBAF in THF afforded the desired starting compound enediol **1** (Scheme 2). As the outset, we attempted the coupling of **1** with benzaldehyde using several Lewis and Brønsted acids in different solvents at various temperatures (Table 1). Lewis acids such as $In(OTf)_3$, $Sc(OTf)_3$, $Cu(OTf)_2$, $InBr_3$, and $InCl_3$ gave the product in low yields (Table 1, entries a–e). No significant improvement in yield was observed even by increasing the catalyst loading (Table 1, entry b). However, the use of 10 mol% $BF_3 \cdot OEt_2$ at 0 °C gave the expected product in 85% yield as a stereoselective manner (entry g, Table 1), In addition, TMSOTf was also found to be equally effective. Alternatively, Brønsted acid such as *p*-TSA was unsuccessful even at elevated temperature after a long reaction time (Table 1, entry f). After several

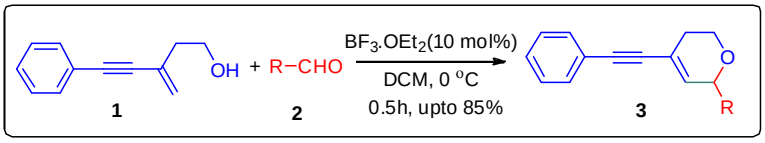
experiments, $BF_3 \cdot OEt_2$ gave the best results in terms of conversion. Among different solvents, DCM was found to be the best for this cyclization.

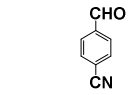
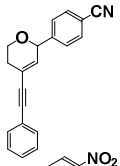
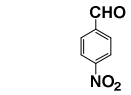
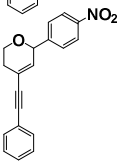
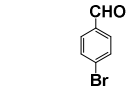
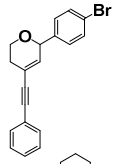
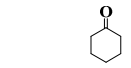
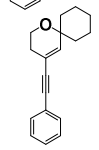
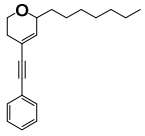
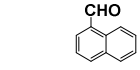
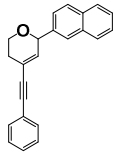
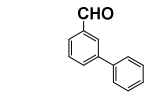
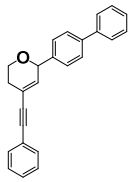
Table 1: Optimisation of reaction

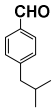
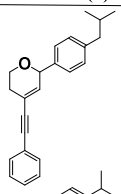
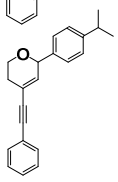
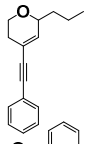
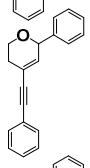
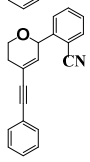
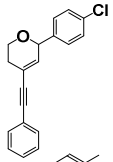
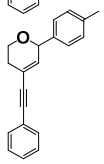
Entry	Lewis acid	mol%	Temp(°C)	Time(h)	(%)yield[b]
a	$In(OTf)_3$	10	25	4.0	35
b	$Sc(OTf)_3$	10	25	6.0	40
c	$Cu(OTf)_2$	10	25	6.0	15
d	$InBr_3$	10	25	5.5	25
e	$InCl_3$	10	25	4.5	20
f	*p-TSA*	20	80	6.0	_
g	$BF_3 \cdot OEt_2$	10	0	0.5	85
h	TMSOTf	10	0	0.5	70

[a]*Reactions was performed at 0.5 mmol scale.* [b]*Yield refers to pure products.*

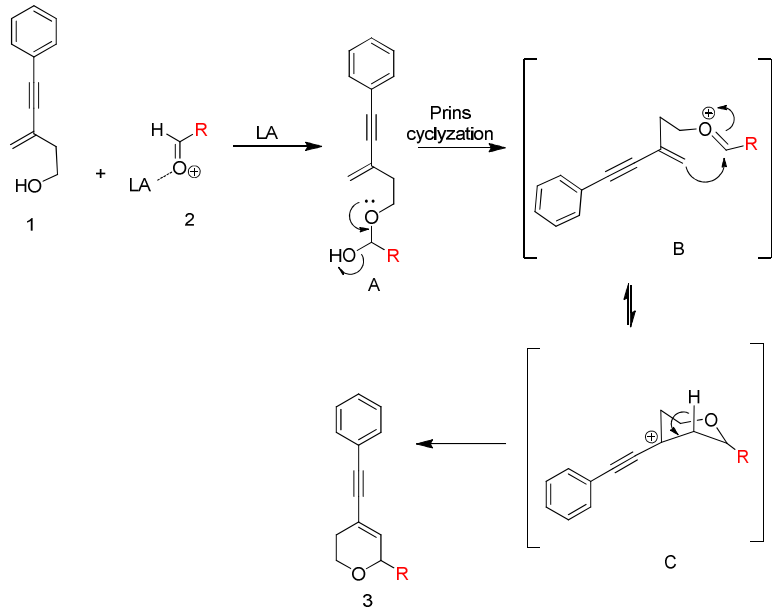
Table 2: Synthesis of 3,6-dihydro-2H-pyran scaffolds



Entry	Aldehyde (6)	Product (7)	yield (%)
a			86
b			87
c			82
d			83
e			80
f			78
g			78

Entry	Aldehyde (4)	Product (5)	yield (%)
h			83
i			83
j			83
k			85
l			77
m			80
n			83

All products were characterized by NMR, IR, and Mass spectrometry
Yield refers to the pure products after chromatography



Plausible reaction mechanism

These results prompted us to investigate this reaction further with various aldehydes bearing a diverse substitution pattern (Table 2). It is worth mentioning that a wide range of functional groups are well tolerated under these reaction conditions . The substituent present on the aromatic ring had shown a modest effect on the conversion. It was observed that both electron rich and electron deficient aldehydes gave the products in comparatively lower yields than the corresponding halogenated or alkyl substituted aromatic aldehydes. Furthermore, the reaction was also quite successful with aliphatic aldehydes such, octanaldehyde and butyraldehyde (Table 2, entries e and j), but relatively in lower yields than aromatic counter parts. The scope of the reaction was further extended to ketones. Interestingly, cyclohexanone gave the desired product in good yield with high selectivity (entry d, Table 2). Furthermore, substituted enediols such as 5-chloro-, and 5-metyl derivatives participated effectively in this cyclization (entries m and n, Table 2).

Based on our earlier observation, we propose a plausible reaction pathway. The reaction is likely to proceed *via* first nucleophilic attack of homoallyl alcohol **1** over activated aldehyde **2** led to form an intermediate oxocarbenium ion **B**, which was subsequently trapped by an olefin to generate *in situ* formed tertiary carbocation **C**. This tertiary carbocation **C,** then *via* regioselective elimination of alpha hydrogen leading to the formation of dihydropyran derivatives **3**.

CONCLUSION

In summary, we have developed mild and efficient method for the synthesis 6-phenyl-4-(phenylethynyl)-3,6-dihydro-2H-pyran *via* Prins cyclization reaction in good yields. This is the first report for the synthesis of 6-phenyl-4-(phenylethynyl)-3,6-dihydro-2H-pyran scaffolds via Prins cyclization protocol.

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