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Efficient Synthesis of 2-Substituted 2,3-Dihydro-4-quinolones as Potential Intermediates for 2-Substituted 1,2,3,4-Tetrahydro-4-quinolone Antitumor Agents

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An efficient method for the synthesis of optically active 2-substituted 2,3-dihydro-4-quinolones has been developed. The key features include the introduction of a chiral side chain and the construction of quinolone skeleton by Mitsunobu alkylation and hydroarylation, respectively.

Key words: 2,3-Dihydro-4-quinolone, 1,2,3,4-Tetrahydro-4-quinolone, Hydroarylation, Mitsunobu, $PtCl_4$, Antitumor agent

INTRODUCTION

2-Substituted chroman-4-one (**1**) is found in many natural products showing various biological activities, such as antitumor (Formica *et al.*, 1995), antibacterial (Hamilton-miller, 1995), anti-inflammatory and antioxidant effects (Miura *et al.*, 1995). The aza-analogs, 2-substituted hydro-4-quinolones (**2**) (Larsen, 2005), have emerged as a novel class of synthetic molecules and drawn the attention of medicinal chemists due to their unique biological activities. Several 2-aryl-1,2,3,4-tetrahydro-4-quinolones (R_2 = aryl, **2a**) have been evaluated for their interactions with tubulin and cytotoxic activity against a panel of human tumor cell lines (Xia *et al.*, 1998). The compounds showed potent cytotoxic and antimitotic antitumor activities due to their antitubulin effects. The drug-tubulin interaction was significantly affected by the configurational and conformational changes in the bicyclic system (Xia *et al.*, 1998). Moreover, single enantiomers were more active than racemates. These considerations prompted us to design and synthesize a novel series of optically active 2-alkyl/aryl-2,3-dihydro-4-quinolone derivatives (**2b**) as potential intermediates for 2-substituted-1,2,3,4-tetrahydro-4-quinolone antitumor agents.

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MATERIALS AND METHODS

All reagents were obtained from Aldrich Chemical (www.sigma-aldrich.com) and used without further purification. Unless otherwise indicated, anhydrous solvents were distilled over CaH_2 or sodium benzophenone ketyl prior to use. TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate ($KMnO_4$) or cerium ammonium molybdenate (CAM). Column chromatography was performed on E. Merck 230-400 mesh silica gel 60. NMR spectra were recorded on Varian Unity 400 instruments at 24°C. Chemical shifts are expressed in ppm relative to TMS (^1H, 0 ppm), $CDCl_3$ (^{13}C, 77.0 ppm); coupling constants are expressed in Hz. Optical rotations were measured using sodium light (D line 589.3 nm). High resolution mass spectra (HRMS) were recorded using EI or CI.

N-Phenylmethanesulfonamide (4a)

Methanesulfonyl chloride (1.93 mL, 25.0 mmol) was added to a cooled solution (0°C) of aniline (1.89 mL, 20.8 mmol) and pyridine (51.0 mL, 62.4 mmol) in anhydrous CH_2Cl_2 (30 mL). The resulting pink solution was stirred at 0°C, with the addition of water (100 mL) at 0°C after 1 h. The aqueous layer was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography, using 1:1 hexane/EtOAc as the eluent, to afford **4a** as a white solid, with a yield of 3.28 g; 92%. TLC: R_f 0.76 (1:1

hexane/EtOAc). mp: 100.4-102.4°C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35 (t, 2H, *J* = 7.6), 7.25 (d, 2H, *J* = 7.6), 7.19 (t, 1H, *J* = 7.6), 7.09 (brs, 1H), 3.02 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 136.9, 130.0, 125.6, 121.0, 39.4.

N-(4-Methoxyphenyl)-methanesulfonamide (4b)

N-(4-methoxyphenyl)-methanesulfonamide was obtained from **3b** using the same procedure described for **4a**, affording **4b** as a white solid, with a yield 84%. TLC: R_f 0.76 (1:1 hexane/EtOAc). mp: 119.5-121.4°C. H-NMR (400 MHz, $CDCl_3$): δ 7.19 (d, 2H, *J* = 9.2), 6.89 (d, 2H, *J* = 9.2), 6.28 (brs, 1H), 3.81 (s, 3H), 2.95 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 158.4, 129.1, 125.1, 115.1, 55.7, 39.2.

N-(4-Fluorophenyl)-methanesulfonamide (4c)

N-(4-fluorophenyl)-methanesulfonamide was obtained from **3c** using the same procedure described for **4a**, to afford **4c** as a white solid, with a yield of 76%. TLC: R_f 0.76 (1:1 hexane/EtOAc). mp: 105.4-106.4°C. H-NMR (400 MHz, $CDCl_3$): δ 7.25 (m, 2H), 7.09 (brs, 1H), 7.06 (m, 2H), 2.99 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 161.0 (d, *J* = 244), 132.7 (d, *J* = 3.1), 124.1 (d, *J* = 8.4), 116.7 (d, *J* = 22.8), 39.3.

N-(2-Methylphenyl)-methanesulfonamide (4d)

N-(2-methylphenyl)-methanesulfonamide was obtained from **3d** using the same procedure described for **4a**, to afford **4d** as a white solid, with a yield of 93%. TLC: R_f 0.71 (1:1 hexane/EtOAc). mp: 105.4-107.2°C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44 (d, 1H, *J* = 8.0), 7.21 (m, 2H), 7.13 (t, 1H, *J* = 8.0), 6.66 (brs, 1H), 3.01 (s, 3H), 2.34 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 134.9, 131.4, 131.1, 127.4, 126.4, 123.4, 39.9, 18.2.

N-(3,5-Dimethoxyphenyl)-methanesulfonamide (4e)

N-(3,5-dimethoxyphenyl)-methanesulfonamide was obtained from **3e** using the same procedure described for **4a**, to afford **4e** as a white solid, with a yield of 99%. TLC: R_f 0.31 (2:1 hexane/EtOAc). mp: 95.8-97.8°C. ^{1}H–NMR (400 MHz, $CDCl_3$): δ 6.90 (brs, 1H), 6.41 (d, 2H, *J* = 2.0), 6.28 (d, 1H, *J* = 2.0), 3.78 (s, 6H), 3.03 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 161.8, 138.8, 98.8, 97.4, 55.7, 39.3.

N-[(1*S*)-1-*n*-Pentyl-2-propynyl]-methanesulfonanilide (5a)

Diethyl azodicarboxylate (283 mL, 1.8 mmol) was added dropwise to a cooled solution (0°C) of **4a** (256 mg, 1.5 mmol), PPh_3 (477 mg, 1.8 mmol) and (*R*)-(+)-1-octyn-3-ol (221 mL, 1.5 mmol) in anhydrous THF (8 mL). The resulting yellow solution was stirred at 0°C for 0.5 h, warmed to room temperature and then stirred for an additional 1 h, after which the solvent was evaporated. The residue was purified by silica gel column chromatography, using 5:1 hexane/EtOAc as eluent, to afford **5a** as a yellow oil, with a yield of 420 mg; 100%. TLC: R_f 0.29 (5:1 hexane/EtOAc). $[\alpha]_D^{25}$ = +42.2 (*c* 0.99, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.57-7.52 (m, 2H), 7.42-7.36 (m, 3H), 4.96 (td, 1H, *J* = 7.4, 2.4), 3.03 (s, 3H), 2.54 (d, 1H, *J* = 2.4), 1.54-1.38 (m, 4H), 1.31-1.15 (m, 4H), 0.83 (t, 3H, *J* = 6.9). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 136.6, 130.7, 129.4, 129.1, 83.1, 74.5, 50.9, 38.6, 34.4, 31.2, 25.7, 22.6, 14.1. HRMS (FAB): calcd for $C_{15}H_{22}NO_2S$ ($[M+H]^+$), 280.1371; found, 280.1367.

N-[(1*R*)-1-Phenyl-2-propynyl]-methanesulfonanilide (5b)

Diethyl azodicarboxylate (283 mL, 1.8 mmol) was added dropwise to a cooled solution (0°C) of **4a** (256 mg, 1.5 mmol), PPh_3 (477 mg, 1.8 mmol) and (*S*)-1-phenyl-2-propyn-1-ol (187 mL, 1.5 mmol) in anhydrous THF (8 mL). The resulting yellow solution was stirred at 0°C for 0.5 h, warmed to room temperature and then stirred for an additional 1 h, after which the solvent was evaporated. The residue was purified by silica gel column chromatography, using 5:1 hexane/EtOAc as eluent to afford **5b** as a yellow oil, with a yield of 232 mg; 54%. TLC: R_f 0.22 (5:1 hexane/EtOAc). $[\alpha]_D^{25}$ = -30.9 (*c* 1.06, MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39-7.38 (m, 2H), 7.25-7.20 (m, 8H), 6.40 (d, 1H, *J* = 2.8), 3.14 (s, 3H), 2.78 (d, 1H, *J* = 2.8). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 136.1, 135.3, 131.3, 129.0, 129.0, 128.8, 128.7, 128.5, 80.6, 77.2, 54.7, 39.5.

N-[(1*R*)-1-(4-Methoxyphenyl)-2-propynyl]-methanesulfonanilide (5c)

N-[(1*R*)-1-(4-methoxyphenyl)-2-propynyl]-methanesulfonanilide was obtained from **4b** using the same procedure described for **5b** to afford **5c**, with a yield of 74%. TLC: R_f 0.46 (4:1 hexane/EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.37 (m, 2H), 7.26-7.22 (m, 3H), 7.09 (d, 2H, *J* = 9.2), 6.71 (d, 2H, *J* = 9.2), 3.72 (s, 3H), 3.11 (s, 3H), 2.77 (d, 1H, *J* = 2.4). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.8, 135.4, 132.5, 128.7, 128.6, 128.5, 128.3 114.2, 80.6, 77.0, 55.4, 54.6, 39.4.

N-[(1*R*)-1-(4-Fluorophenyl)-2-propynyl]-methanesulfonanilide (5d)

N-[(1*R*)-1-(4-fluorophenyl)-2-propynyl]-methanesulfonanilide was obtained from **4c** by the same procedure described for **5b**, to afford **5d**, with a yield of 67%. TLC: R_f 0.28 (4:1 hexane/EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39-7.36 (m, 2H), 7.27-7.23 (m, 3H), 7.17 (dd, 2H, *J* = 8.8, 5.2), 6.89 (dd, 2H, *J* = 8.8, 8.0), 6.38 (d, 1H, *J* = 2.4), 3.12 (s, 3H), 2.80 (d, 1H, *J* = 2.4). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 163.9, 161.5, 135.0, 133.1 (d, J = 8.4), 131.9 (d, J = 3.0), 128.8, 128.6 (d, J = 8.4), 125.9 (d, J = 22), 80.3,

77.4, 54.7, 39.4.

N-[(1*R*)-1-(2-Methylphenyl)-2-propynyl]-methanesulfonanilide (5e)

N-[(1*R*)-1-(2-methylphenyl)-2-propynyl]-methanesulfonanilide was obtained from **4d** using the same procedure described for **5b**, to afford **5e**, with a yield of 54%. TLC: R_f 0.32 (4:1 hexane/EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.81 (dd, 1H, *J* = 7.6, 2.0), 7.25-7.15 (m, 7H), 7.00 (m, 1H), 6.30 (d, 1H, *J* = 2.4), 3.19 (s, 3H), 2.76 (d, 1H, *J* = 2.4). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 142.2, 134.9, 131.9, 131.5, 129.7, 128.5, 129.4, 128.9, 128.3, 126.2, 81.3, 76.7, 55.2, 38.9, 18.2.

N-[(1*R*)-1-(3,5-Dimethoxyphenyl)-2-propynyl]methanesulfonanilide (5f)

N-[(1*R*)-1-(3,5-dimethoxyphenyl)-2-propynyl]-methanesulfonanilide was obtained from **4e** using the same procedure described for **5b**, to afford **5f**, with a yield of 44%. TLC: R_f 0.64 (2:1 hexane/EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.43 (m, 2H), 7.25 (m, 3H), 6.35 (m, 4H), 3.62 (s, 6H), 3.16 (s, 3H), 2.78 (d, 1H, *J* = 2.0). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 160.5, 137.7, 135.3, 128.8, 128.7, 128.5, 109.4, 101.2, 80.5, 77.1, 55.5, 54.7, 39.5.

(2*S*)-1,2-Dihydro-1-methanesulfonyl-2-*n*-pentylquinoline (6a)

A solution of *N*-propargylaniline **5a** (28 mg, 0.1 mmol) in anhydrous dichloroethane (1 mL, 0.1 M) was added to $PtCl_4$ (3.4 mg, 0.01 mmol). The reaction mixture was stirred at 70°C for 2 h under N_2. The solvent was then removed *in vacuo*. Silica gel column chromatography, using 6:1 hexane/EtOAc as eluent, afforded pure dihydroquinoline **6a**, with a yield of 20 mg; 72%. TLC: R_f 0.27 (6:1 hexane/EtOAc). $[\alpha]_D^{25}$ = +287 (*c* 1.0, MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.61 (d, 1H, *J* = 7.2), 7.27 (td, 1H, *J* = 7.2, 1.6), 7.22 (td, 1H, *J* = 7.2, 1.6), 7.14 (dd, 1H, *J* = 7.2, 1.6), 6.53 (d, 1H, *J* = 9.6), 6.08 (dd, 1H, *J* = 9.6, 5.6), 4.72 (m, 1H), 2.65 (s, 3H), 1.49-1.34 (m, 4H), 1.32-1.17 (m, 4H), 0.85 (t, 3H, *J* = 7.2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 133.1, 130.1, 128.6, 128.5, 127.8, 126.9, 126.8, 125.0, 55.4, 37.7, 33.2, 31.5, 25.0, 22.6, 14.2. HRMS (FAB): calcd for $C_{15}H_{22}NO_2S$ ($[M+H]^+$), 280.1371; found, 280.1374.

(2*R*)-1,2-Dihydro-1-methanesulfonyl-2-phenylquinoline (6b)

A solution of *N*-propargylaniline **5b** (28 mg, 0.1 mmol) in anhydrous dichloroethane (1 mL, 0.1 M) was added to $PtCl_4$ (3.4 mg, 0.01 mmol). The reaction mixture was stirred at 70°C for 2 h under N_2. The solvent was then removed *in vacuo*. Silica gel column chromatography, using 5:1 hexane/EtOAc as eluent, afforded pure dihydroquinoline **6b**, with a yield of 16.9 mg; 60%. TLC: R_f 0.21 (5:1 hexane/EtOAc). $[\alpha]_D^{25}$ = +374 (*c* 1.0, CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.53 (dm, 1H, *J* = 7.6), 7.33 (m, 2H), 7.27-7.18 (m, 6H), 6.80 (d, 1H, *J* = 9.2), 6.30 (dd, 1H, *J* = 9.2, 6.0), 5.99 (d, 1H, *J* = 6.0), 2.76 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 138.4, 133.2, 131.3, 128.9, 128.7, 128.5, 128.3, 127.5, 127.2, 126.9, 126.7, 126.6, 57.2, 38.0.

(2*R*)-1,2-Dihydro-1-methanesulfonyl-6-methoxy-2-phenylquinoline (6c)

A solution of *N*-propargylaniline **5c** (176 mg, 0.56 mmol) in anhydrous dichloroethane (5 mL, 0.1 M) was added to $PtCl_4$ (38 mg, 0.11 mmol). The reaction mixture was stirred at room temperature for 3 h under N_2. The solvent was then removed *in vacuo*. Silica gel column chromatography, using 4:1 hexane/EtOAc as eluent, afforded pure dihydroquinoline **6c**, with a yield of 44 mg; 25%. TLC: R_f 0.21 (4:1 hexane/EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.42 (d, 1H, *J* = 8.8), 7.33-7.30 (m, 2H), 7.26-7.20 (m, 3H), 6.77 (d, 1H, *J* = 9.6), 6.75 (d, 1H, *J* = 2.8), 6.72 (dd, 1H, *J* = 6.8, 2.8), 6.31 (dd, 1H, *J* = 9.6, 6.0), 5.94 (d, 1H, *J* = 6.0), 3.77 (s, 3H), 2.72 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 158.3, 138.2, 129.4, 128.9, 128.7, 128.2, 128.1, 127.6, 126.8, 125.9, 113.9, 112.0, 57.2, 55.6, 37.4.

(2*R*)-1,2-Dihydro-6-fluoro-1-methanesulfonyl-2-phenylquinoline (6d)

A solution of *N*-propargylaniline **5d** (72.8 mg, 0.24 mmol) in anhydrous dichloroethane (2.4 mL, 0.1 M) was added to $PtCl_4$ (8.1 mg, 0.024 mmol). The reaction mixture was stirred at 70°C for 15 h under N_2. The solvent was then removed *in vacuo*. Silica gel column chromatography, using 4:1 hexane/EtOAc as eluent, afforded pure dihydroquinoline **6d**, with a yield of 22.4 mg; 31%. TLC: R_f 0.27 (4:1 hexane/EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.49 (dd, 1H, *J* = 9.6, 5.2), 7.31 (m, 2H), 7.29-7.22 (m, 3H), 7.68 (m, 2H), 6.78 (d, 1H, *J* = 9.2), 6.38 (dd, 1H, *J* = 9.2, 5.6), 5.99 (d, 1H, *J* = 5.6), 2.75 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 162.4, 159.9, 137.8, 130.0 (d, *J* = 9.1), 129.4 (d, *J* = 9.1), 129.1, 128.8, 128.4, 127.5, 126.1 (d, *J* = 1.5), 115.6 (d, *J* = 23), 113.2 (d, *J* = 23), 57.2, 37.8.

(2*R*)-1,2-Dihydro-1-methanesulfonyl-8-methyl-2-phenylquinoline (6e)

A solution of *N*-propargylaniline **5e** (28.5 mg, 0.1 mmol) in anhydrous dichloroethane (1 mL, 0.1 M) was added to $PtCl_4$ (5.5 mg, 0.014 mmol). The reaction mixture was stirred at 70°C for 21 h under N_2. The solvent was then removed *in vacuo*. Silica gel column chromatography, using 3:1 hexane/EtOAc as eluent, afforded pure dihydroquinoline **6e**, with a yield of 10.8 mg; 38%. TLC: R_f 0.20 (3:1 hexane/EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.29 (m, 2H), 7.25-7.21 (m, 3H), 7.13 (t, 1H, *J* = 7.6), 7.07 (dd, 1H, *J* = 7.6, 1.2), 7.01 (dd, 1H, *J* = 7.6, 1.2), 6.86 (dd,

1H, J = 9.6, 1.2), 6.34 (dd, 1H, J = 9.6, 6.4), 5.88 (d, 1H, J = 6.4), 2.79 (s, 3H), 2.26 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 139.4, 137.1, 131.7, 130.9, 130.2, 128.6, 128.3, 128.2, 127.9, 127.6, 124.2, 124.1, 57.8, 37.7, 19.4.

(2*R*)-1,2-Dihydro-1-methanesulfonyl-5,7-dimethoxy-2-phenylquinoline (6f)

A solution of *N*-propargylaniline **5f** (149 mg, 0.43 mmol) in anhydrous dichloroethane (4 mL, 0.1 M) was added to $PtCl_4$ (29 mg, 0.086 mmol). The reaction mixture was stirred at room temperature for 5 h under N_2. The solvent was then removed *in vacuo*. Silica gel column chromatography, using 4:1 hexane/EtOAc as eluent afforded pure dihydroquinoline **6f**, with a yield of 65.2 mg; 42%. TLC: R_f 0.27 (4:1 hexane/EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35 (d, 2H, J = 8.8), 7.27-7.21 (m, 3H), 7.07 (d, 1H, J = 10.0), 6.76 (d, 1H, J = 2.8), 6.29 (d, 1H, J = 2.0), 6.10 (dd, 1H, J = 9.6, 6.0), 5.95 (d, 1H, J = 6.0), 3.82 (s, 3H), 3.76 (s, 3H), 2.77 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 160.4, 156.1, 138.8, 134.9, 128.6, 128.1, 127.6, 122.4, 120.9, 111.5, 103.7, 97.2, 56.8, 55.8, 55.7, 38.1.

(2*S*)-1,2,3,4-Tetrahydro-1-methanesulfonyl-2-*n*-pentylquinoline (7a)

A solution of **6a** (28 mg, 0.1 mmol) and 5 wt.% Pd-C (3.5 mg) in EtOH (1 mL) was stirred at room temperature under H_2 atmosphere for 3 h, after which the solvent was evaporated. Silica gel column chromatography, using 5:1 hexane/EtOAc as eluent afforded **7a** as a yellow oil, with a yield of 24 mg; 85%. TLC: R_f 0.18 (6:1 hexane/EtOAc). $[\alpha]_D^{25}$ = +31.3 (*c* 1.0, MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, J = 8.4), 7.19 (td, 1H, J = 8.4, 2.4), 7.15-7.08 (m, 2H), 4.40 (m, 1H), 2.83 (s, 3H), 2.75 (m, 2H), 2.16 (m, 1H), 1.75 (m, 1H), 1.57 (m, 1H), 1.44-1.35 (m, 3H), 1.33-1.26 (m, 4H), 0.85 (t, 3H, J = 7.2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 135.5, 130.9, 129.3, 127.1, 125.7, 125.4, 55.5, 39.0, 33.5, 31.7, 27.1, 25.8, 24.2, 22.7, 14.2. HRMS (FAB): calcd for $C_{15}H_{23}NO_2S$ (M^+), 281.1450; found, 281.1445.

(2*R*)-1,2,3,4-Tetrahydro-1-methanesulfonyl-2-phenylquinoline (7b)

A solution of **6b** (16 mg, 0.056 mmol) and 5 wt.% Pd-C (3.5 mg) in EtOH (1 mL) was stirred at room temperature under H_2 atmosphere for 2 h, after which the solvent was evaporated. Silica gel column chromatography, using 5:1 hexane/EtOAc as eluent afforded **7b** as a colorless oil, with a yield of 15.5 mg; 96%. TLC: R_f 0.27 (5:1 hexane/EtOAc). $[\alpha]_D^{25}$ = +87.5 (*c* 0.7, MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.73 (d, 1H, J = 8.0), 7.30-7.20 (m, 6H), 7.13–7.07 (m, 2H), 5.54 (t, 1H, J = 6.4), 2.85 (s, 3H), 2.70 (m, 2H), 2.49 (m, 1H), 2.07 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 142.0, 136.7, 131.7, 129.0, 128.9, 127.5, 127.4, 126.4, 124.9, 123.7, 59.5, 39.7, 31.8, 25.6.

(2*S*)-2,3-Dihydro-1-methanesulfonyl-2-*n*-pentyl-4-quinolone (8a)

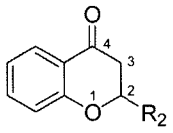
A solution of $CuSO_4$ (214 mg, 0.67 mmol) and $K_2O_8S_2$ (36.2 mg, 0.067 mmol) in H_2O (1 mL) was added to a solution of **7a** (23.6 mg, 0.0838 mmol) in CH_3CN (1 mL). The blue suspension was stirred at 70 °C for 18 h, after which the solvent was removed *in vacuo*. The aqueous layer was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography, using 3:1 hexane/EtOAc as eluent, to afford **8a** with a yield of 7.0 mg; 23%. TLC: R_f 0.28 (3:1 hexane/EtOAc). $[\alpha]_D^{25}$ = +9.54 (*c* 1.1, MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.04 (ddd, 1H, J = 8.0, 1.6, 0.4), 7.76 (ddd, 1H, J = 8.0, 1.6, 0.4), 7.58 (td, 1H, J = 8.0, 1.6), 7.28 (td, 1H, J = 8.0, 1.6), 4.76 (m, 1H), 3.09 (dd, 1H, J = 17.6, 6.0), 3.03 (s, 3H), 2.67 (dd, 1H, J = 17.6, 1.6), 1.62 (m, 1H), 1.48 (m, 1H), 1.37 (m, 2H), 1.24 (m, 4H), 0.84 (t, 3H, J = 7.2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 192.6, 139.9, 135.5, 127.9, 126.0, 125.6, 124.4, 56.4, 42.7, 40.7, 32.6, 31.3, 26.2, 22.6, 14.1.

(2*R*)-2,3-Dihydro-1-methanesulfonyl-2-phenyl-4-quinolone (8b)

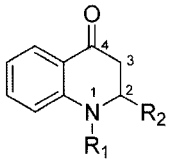
A solution of $CuSO_4$ (69.0 mg, 0.432 mmol) and $K_2O_8S_2$ (12.0 mg, 0.043 mmol) in H_2O (1 mL) was added to a solution of **7b** (15.5 mg, 0.054 mmol) in CH_3CN (1 mL). The blue suspension was stirred at 70°C for 8 h. The solvent was then removed *in vacuo*. The aqueous layer was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography, using 3:1 hexane/EtOAc as eluent, to afford **8b**, with a yield of 3.3 mg; 20%. TLC: R_f 0.34 (2:1 hexane/EtOAc). $[\alpha]_D^{25}$ = +28.5 (*c* 0.2, CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.98 (dd, 1H, J = 8.0, 4.0), 7.79 (dm, 1H, J = 8.0), 7.54 (ddd, 1H, J = 8.0, 7.2, 4.0), 7.25-7.17 (m, 6H), 6.04 (dd, 1H, J = 5.6, 2.4), 3.38 (dd, 1H, J = 17.6, 5.6), 3.31 (dd, 1H, J = 17.6, 2.4) 3.11 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 192.0, 137.9, 137.6, 135.7, 129.1, 129.0, 128.3, 128.1, 126.9, 125.2. 123.0, 58.3, 42.4, 40.9.

RESULTS AND DISCUSSION

While there are extensive literature precedents for the syntheses of 2-substituted chroman-4-ones and 2-substituted 2,3-dihydro-4-quinolones, few are amenable for the synthesis of single enantiomers. Recently, Tamio Hayashi reported the first catalytic enantioselective synthesis of 2-aryl-2,3-dihydro-4-quinolones using rhodium-catalyzed asymmetric 1,4-addition of arylzinc reagents to 4-quinolones (Shintani *et al.*, 2005). Herein is reported a



2-Substituted chroman-4-one
(R_2 = aryl or alkyl; **1**)



2-Substituted 1,2,3,4-tetrahydro-4-quinolone
(R_1 = H, R_2 = aryl or alkyl; **2a**)
2-Substituted 2,3-dihydro-4-quinolone
(R_1 = SO_2R, R_2 = aryl or alkyl; **2b**)

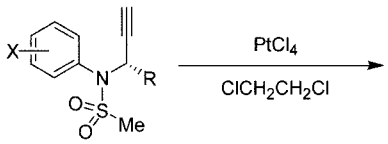
Fig. 1. Structures of 2-substituted chroman-4-one (**1**) and 2-substituted hydro-4-quinolones (**2**)

flexible synthetic route for the development of optically active 2-substituted 2,3-dihydro-4-quinolones, which is applicable to both C2-alkyl and C2-aryl analogs.

Recently, a novel strategy for the preparation of optically active 2-substituted dihydroquinolines has been developed and applied for a concise synthesis of (+)-(*S*)-angustureine in our laboratory (Ryu, 2006). In the context of this effort, we have extended this strategy for the syntheses of 2-substituted-2,3-dihydro-4-quinolones. As shown in Scheme 1, the syntheses of hydroarylation precursors (**5a-f**) were accomplished in a two-step sequence, which was initiated by the *N*-methanesulfonylation of aniline with MsCl, affording **4a-e** with yields between 76 and 99%. A chiral side chain was introduced using the Mitsunobu condition with (*R*)-(+)-1-octyn-3-ol or (*S*)-1-phenyl-2-propyn-1-ol in the presence of Ph_3P/DEAD. The reaction proceeded cleanly to provide *N*-mesylpropargylanilides, **5a-f**. The sulfonamide served as an efficient nucleophile in the Mitsunobu alkylation step, as well as an arene-free protecting group in the next hydroarylation step. The cyclization precursors **5a** and **5b** were then subjected to various hydroarylation conditions, such as Hg (II) (Nishizawa *et al.*, 2003), Pt (II) (Pastine *et al.*, 2003a), Pt (IV) (Pastine *et al.*, 2003b) and Au (III) (Shi *et al.*, 2004). The dihydroquinolines **6a** and **6b** were readily obtained in yields between 60 and 72% employing Pt (IV)-catalyzed hydroarylation, but the other catalytic conditions employed proved to be ineffective. It should be noted that the catalytic hydroarylation, without activation by electron-donating groups on the arene, has; thus far, proved to be problematic. With respect to the above, this hydroarylation strategy has been verified for various substrates, **5c-f** (Table I).

Subsequent hydrogenation of the dihydroquinolines **6a**

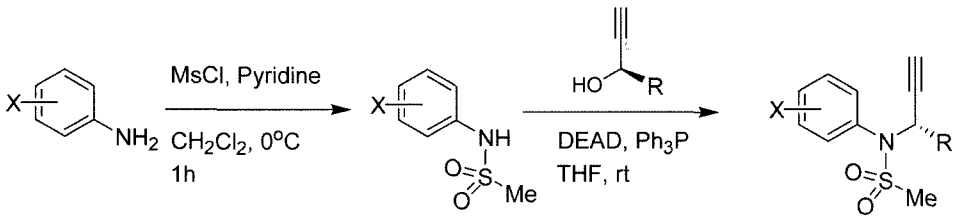
Table I. Hydroarylation of *N*-mesylpropargylanilide (**5a-f**)



5a (X = H, R = *n*-pentyl)
5b (X = H, R = Ph)
5c (X = 4-MeO, R = Ph)
5d (X = 4-F, R = Ph)
5e (X = 2-Me, R = Ph)
5f (X = 3,5-di*MeO*, R = Ph)

6a (X = H, R = *n*-pentyl)
6b (X = H, R = Ph)
6c (X = 4-MeO, R = Ph)
6d (X = 4-F, R = Ph)
6e (X = 2-Me, R = Ph)
6f (X = 3,5-di*MeO*, R = Ph)

Entries	Alkynes	Dihydroquinolines	Temp. (°C)	Time (h)	Yield (%)
1	**5a**	**6a**	70	2	72
2	**5b**	**6b**	70	2	60
3	**5c**	**6c**	rt	3	25
4	**5d**	**6d**	70	15	31
5	**5e**	**6e**	70	21	38
6	**5f**	**6f**	rt	5	42

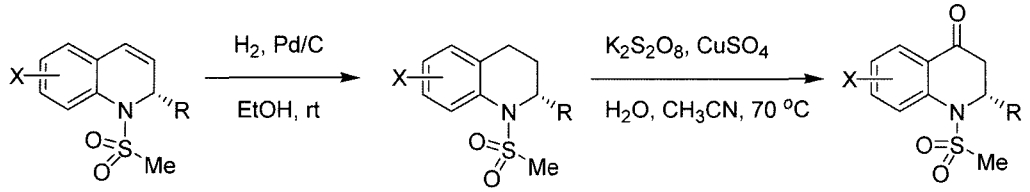


3a (X = H)
3b (X = 4-MeO)
3c (X = 4-F)
3d (X = 2-Me)
3e (X = 3,5-diMeO)

4a (X = H, 92%)
4b (X = 4-MeO, 84%)
4c (X = 4-F, 76%)
4d (X = 2-Me, 93%)
4e (X = 3,5-diMeO, 99%)

5a (X =H, R = *n*-pentyl, 100%)
5b (X = H, R = Ph, 54%)
5c (X = 4-MeO, R = Ph, 74%)
5d (X = 4-F, R = Ph, 67%)
5e (X = 2-Me, R = Ph, 54%)
5f (X = 3,5-diMeO, R = Ph, 44%)

Scheme 1. Syntheses of *N*-mesylpropargylanilide (**5a-f**)



6a (X = H, R = *n*-pentyl) **7a** (X = H, R = *n*-pentyl, 85%) **8a** (X = H, R = *n*-pentyl, 23%)
6b (X = H, R = Ph) **7b** (X = H, R = Ph, 96%) **8b** (X = H, R = Ph, 20%)

Scheme 2. Syntheses of 2-substituted-2,3-dihydro-4-quinolones (**8a** and **8b**)

and **6b** under 5% Pd/C condition afforded the tetrahydroquinolines **7a** and **7b**, with yields between 85 and 96% (Scheme 2). Finally, treatment of **7a** and **7b** with eight equivalents of copper sulfate and 80 mol% peroxydisulfate in aqueous acetonitrile at 70°C yielded the 2-substituted-2,3-dihydro-4-quinolones, **8a** and **8b**.

In summary, a flexible route for the synthesis of optically active 2-alkyl/aryl-2,3-dihydro-4-quinolones has been demonstrated. The chiral alkyl/aryl side chain was introduced using Mitsunobu alkylation, with the quinolone skeleton constructed using hydroarylation and benzylic oxidation. Currently, this route is being extended for the syntheses of optically active analogs containing a variety of substituents at the N1 and C2 positions.

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