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The unique structural and activity of the compactin as hypocholesterlemic agent, have aroused to synthesize challenging target

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ABSTRACT

Hypercholesterolemia is a primary risk factor in coronary heart disease which is the major cause of deaths in the Western World. Clinical studies with lipid lowering agents have established that lowering elevated serum cholesterol levels reduces the incidence of cardiovascular mortality. In humans, more than one-half of total body cholesterol is derived from *de novo* synthesis. The rate-limiting step in cholesterol biosynthesis is the reduction of HMG CoA to mevalonic acid. There is the attractive possibility that compactin or some related compound might be useful as a hypocholesterlemic agent.

Keynote: The synthetic strategy involves chiral propargyl alcohol from 2, 3-epoxy chloride acetylinic fragment, Ethyl chloroformate, Lindlar's hydrogenation, Diel's-Alder reaction.

INTRODUCTION

Coronary heart disease actually is a wide assortment of diseases. This is caused when fatty deposits called plaque buildup on the inner walls of arteries. Many scientists believe that a high level of cholesterol in the blood is a major contributor to the development of atherosclerosis. Since in humans the greater part of the cholesterol in the body is synthesized *de novo* mostly in the liver, the search for drug to inhibit cholesterol biosynthesis, has long been pursued as a means to lower the level of plasma cholesterol and so help to prevent and treat. One of the major causes of death in the U.S. and other developing countries is coronary heart disease [1].

Hypercholesterolemia is a primary risk factor in coronary heart disease, which is the major cause of deaths in the Western World [2]. Clinical studies with lipid lowering agents have established that lowering elevated serum cholesterol levels reduces the incidence of cardiovascular mortality [3]. Endo and his associates at Sankyo Co. (Tokyo), who had tested 8000 strains of microorganisms for their ability to produce an inhibitor of sterol synthesis in *vitro*, first discovered three active compounds designated ML-236A, ML-236B, ML-236C, in the culture broth of fungus *penicillium citrinum*[4]. The affinity of HMG-CoA reductase for the compactin is 10,000-fold higher than its affinity for the natural substrate. Compactin does not affect other enzymes involved in

cholesterol biosynthesis [5]. In addition almost all studies on compactin with cultured cells and intact animals suggest that reductase is the only enzyme that is inhibited by compactin. The decalin ring of compactin related compounds is essential to the inhibitory activity. This is shown by the data that the compounds without decalin ring activity is 10^6-fold less than compactin [6].

At higher concentrations of compactin where sterol synthesis is reduced by over 90%, and also inhibits cell growth [7]. This inhibition can be overcome and cells can grow normally if a small amount of mevalonate is added to the culture medium. These findings strongly suggest that compactin is a specific inhibitor of HMG-CoA reductase. Hypocholesterolemic activity of compactin when given orally is effective in lowering plasma cholesterol levels in man and some animal species, notably the chicken, rabbit, dog and monkey. In other species, such as the rat, mouse, and hamster, the feeding of compactin does not decrease plasma cholesterol. In healthy persons, compactin and mevinolin are well tolerated and exert a rapid and profound cholesterol-lowering effect at a dose of 5-10 mg/ day [8].

EXPERIMENTAL DATA

General procedure and materials

3-(5-methylfuran-2-yl) propanal

To a mixture of 2-methylfuran (17.0 g, 207.3 mmol), acrolein (8.12 g, 103.5 mmol) and hydroxyquinine in 12 mL of water, few drops of glacial acetic acid was added drop wise at 0 ^oC temperature and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was diluted with ether (100 mL) and aqueous layer was separated. The organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed and residue was purified on column chromatography to afford the 3-(5-methylfuran-2-yl) propanal **(1)** as a brown colour oily liquid in 75% of yield (21.0 g).

^{1}H NMR (200 MHz, $CDCl_3$)

δ 9.01 (s, 1H, -CHO), 5.76 (d, J = 5 Hz, 2H), 2.81-2.90 (m, 2H), 2.62-2.78 (m, 2H – CH2-CHO) and 2.20 (s, 3H, CH3).

IR (neat)

3430, 2940, 1716, 1412, 1219, 1130, 1069, 968, 716, 609 cm^{-1}.

Mass

m/z 139 (M^+1).

3-(5-methylfuran-2-yl) propan-1-ol

3-(5-methylfuran-2-yl) propanal (**1**) (21.0 g, 150 mmol) was dissolved in (500 mL) methanol cooled to 0 ^oC, to this $NaBH_4$ (5.5 g, 150 mmol) was added in small portions under nitrogen atmosphere. After complete addition, the reaction mixture was brought to room temperature and allowed to stirred for 1 h. The reaction mixture was quenched with saturated NH_4Cl solution and stirred for additional 1 h, filtered through pad of celite and concentrated under vacuum to yield the crude product, which was purified by column chromatography (Hexanes/EtoAc) to afford the pure product **(2)** (21.0 g 98% yield) as a colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 5.82 (d, *J* = 9 Hz, 2H), 3.60-3.70 (m, 2H), 2.65 (t, J = 12.6 2H, $-CH_2OH$), 2.20 (s, 3H, $-CH_3$) and 1.81-1.02 (m, 3H, $-CH_2-$ and -OH).

IR (neat)

3477, 3411, 2924, 1638, 1570, 1452, 218, 1020, 772, 616 cm^{-1}.

Mass

m/z 163 (M^+ Na).

3-(5-methylfuran-2-yl) propyl-4-methylbenzenesulfonate

Compound **2** (21.0 g, 147 mmol) was dissolved in dry dichloromethane (500 mL) and to this solution triethylamine (17.8 g, 177.4 mmol) was added at 0 ^oC and allowed to stirred for 1 h. Then *p*-toluene sulphonyl chloride (33.8 g, 177.4 mmol) was added in small portions. After completion of the reaction, the reaction mixture was brought to room temperature and stirred for 1 h. The organic layer was washed with water and extracted with DCM (3x200 mL). The layer was washed with brine and dried over $NaSO_4$ and

concentrated under vacuum. The crude product was purified by silica gel column chromatography (20% ethyl acetate in hexane) to give **(3)** (33.0 g in 75% of yield) as colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.81 (d, *J* = 13.2 Hz, 2H, -ArH), 7.32 (d, *J* = 13.2 Hz, 2H –ArH), 5.71 (s, 2H), 4.15 (t, *J* = 9.0 Hz, 2H), 2.65 (t, *J* = 9.0 Hz, 2H) 2.55 (s, 3H, –Ar-CH_3), 2.20 (s, 3H, -CH_3), 1.90-2.02 (m, 2H)

IR (neat)

3447, 2925, 1599, 1448, 1359,1180, 1012, 924, 818, 780, 664.cm^{-1}.

Mass

m/z 318 (M^+ 1).

2-(3-iodopropyl)-5-methylfuran

3-(5-methylfuran-2-yl) propyl 4-methylbenzenesulfonate **(3)** (33.0 g, 111.4 mmol) and KI (55.5 g, 334.4 mmol) in dry acetone (500 mL) was refluxed for 8 h. The dark brownish solution was concentrated under vacuum. The residue was diluted with ethyl acetate, washed successively with saturated sodium thiosulphate solution, water, brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (5% ethyl acetate in hexane) to give compound **4** (26.7 g, 95% yield) as a colorless oily liquid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 5.81 (d, *J* = 19.0 Hz, 2H), 3.22 (t, *J* = 12.0 Hz, 2H), 2.70 (t, *J* = 12.2 Hz, 2H), 2.20, (s, 3H, -CH_3), 2.01-2.21 (m,
2H).

IR (neat)

3427, 2924, 2366, 1569, 1441, 1360, 1286, 1220, 1179, 1100, 1018, 934, 780, 663 cm^{-1}.

Mass

m/z 274.7(M^+ Na).

^{13}CNMR (200 MHz, $CDCl_3$)

δ 153.0, 150.2, 105.5, 106.0, 34.0, 28.0, 16.0, and 6.4.

6-(5-methylfuran-2-yl) hex-2-yn-1-ol

To liquid ammonia in a 50 mL two neck R.B.F equipped with NH_3 condenser was added finely and freshly cut small pieces of lithium metal (0.89 g, 298.8 mmol) and the reaction mixture was stirred for 30 minutes, followed by addition of ferric nitrate (0.025 g). The deep blue colored solution turned gray indicating the formation of lithium amide. Propargyl alcohol (6.6 g, 19.5 mmol) was then added drop wise and the reaction mixture was stirred for 3h at –33 ^{o}C temperature. The compound (**5**) (25 g, 99.6 mmol) dissolved in anhydrous THF was added drop wise and the reaction mixture was stirred for 8 h. To this, solid ammonium chloride was added, portion wise and the ammonia was allowed to evaporate. Ether was added to the solid residue and filtered off. The filtrate was concentrated and purified by column chromatography to give the propargyl alcohol **6** as an orange colored liquid, in 70% of yield (13.0 g).

^{1}H NMR (200 MHz, $CDCl_3$)

δ 5.81 (d, *J* = 4.8 Hz, 2H), 4.22 (s, 2H , CH_2-OH), 3.61 (br, s,1H), 2.70 (t, *J* = 8.0 Hz, 2H), 2.20-2.31 (m, 5H), 1.72-1.82 (m, 2H).

IR (neat)

3453, 2926, 1635, 1219, 772 Cm^{-1}

Mass

m/z 179(M^+1).

^{13}CNMR (200 MHz, $CDCl_3$)

δ 153.1, 150.0, 105.5, 106.0, 86.3, 78.0, 51.0, 28.1, 18.2, 13.7, 13.4.

(E)-6-(5-methylfuran-2-yl) hex-2-en-1-ol

To a slurry of lithium aluminum hydride (1.2 g, 33.3 mmol) in anhydrous THF (100 mL) at 0 ^{o}C was added drop wise a solution of **5** (12.0 g, 66.6 mmol) in THF (30 ml) over a period of 30 minutes. The reaction mixture was allowed to warm to room temperature for 6 h. It was then brought to 0 ^{o}C and quenched with aqueous saturated sodium sulphate solution by drop wise addition. The precipitated solid was filtered and the filtrate was dried over sodium sulphate and concentrated under vacuum. It was purified by column chromatography to get the allylic alcohol **(6)** as a liquid, 11.8 g in 96 % of yield.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 5.81 (s, 2H), 5.61-5.68 (m, 2H), 4.52 (s, 2H), 2.55 (t, *J* = 7.7 Hz, 2H), 2.25 (s, 3H), 2.0-2.14 (m, 3H), 1.61-1.78 (m, 2H), 1,48-1.60 (br, s, 1H)

IR (neat)

3442, 2926, 2897, 1635, 1459, 768 cm^{-1}.

Mass

m/z 199(M^+1).

[α] ^{D}

-17.8^o (C=1.15 $CHCl_3$).

((2S, 3S) -3 - (3- (5- methylfuran- 2 -yl) propyl) oxiran-2-yl) methanol

To a cooled solution of anhydrous CH_2Cl_2 (50 mL) was added 1.0 g of 4 A^o molecular sieves and freshly distilled titanium tetraisopropoxide (17.16 g, 60.4 mmol) at –33 ^{o} C (dry ice / CCl_4), to this freshly distilled (+)-DET (catalytical amount) in anhydrous CH_2Cl_2 (5 ml) was added. The resulting mixture was stirred for 15 minutes and then a solution of compound **(6)** (11.0 g, 60.4 mmol) in dichloromethane (25 ml) was added. 10 minutes later *t*-butyl hydrogen peroxide solution (3.3 M solution in toluene 48 ml 26.5 mmol) was added; the reaction mixture was then stirred at –20 ^{o} C for 6-8 h. The reaction was allowed to warm to 0 ^{o}C and poured into a freshly prepared, cooled (0 ^{o}C) solution of $FeSO_4$ and tartaric acid (1: 3) in de-ionized water (20 mL). The two-phase mixture was obtained. Aqueous phase was separated and extracted with DCM, the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, which was further purified by column chromatography to yield compound **(7)** in 78% (9.5 g).

^{1}H NMR (200 MHz, $CDCl_3$)

δ 5.81 (br, s, 2H,), 3.87 (d, *J* = 3.3 Hz, 1H), 3.53 (d, *J* = 3.3 Hz, 1H), 2.80-3.01 (m, 2H), 2.51 (t, J = 10.0 Hz, 2H), 2.20 (s, 3H), 1.4-1.8 (br, m, 4H)

IR (neat)

3442, 2926, 2897, 1635, 1459, 768 cm^{-1}.

Mass

m/z 199(M^+1).

[α] ^{D}

-17.8^o (C=1.15 $CHCl_3$).

2-(3-((2S, 3R)-3-(chloromethyl) oxiran-2-yl) propyl) -5-methylfuran

To a solution of triphenyl phosphine (12.5 g, 47.9 mmol) in anhydrous CCl_4 (100 mL) was added a solution of (**7**) in CCl_4 (9.5 g, 47.9 mmol) at reflux temperature for 24 h. It was then cooled to room temperature and the solvent was removed in vacuum. The crude product was purified by column chromatography to give compound (**8**) as a colorless liquid in 70% of yield (6.3 g).

^{1}H NMR (200 MHz, $CDCl_3$)

δ 5.8 2 (d, *J* = 2.7 Hz, 2H,), 3.61 (q, $J_{1,2}$ = 10.9 Hz, $J_{1,3}$ = 21.8 Hz, 1H), 3.4 (q, $J_{1,2}$ = 10.9, $J_{1,3}$ = 21.8 Hz, 1H), 2.92-3.01 (m, 1H), 2.8-2.89 (m, 1H), 2.6 (t, *J*= 13.6 Hz, 2H), 2.20 (s, 2H), 1.72-1.85 (m, 2H), 1.58-1.66 (m, 2H)

IR (neat)

2919, 1635, 1469, 1262, 723, 564 cm^{-1}

Mass

m/z 215(M^+1).

[α] ^{D}

-4.58^o (C=1. 5 $CHCl_3$).

(S)-6-(5-methylfuran-2-yl) hex-1-yn-3-ol

To a solution of liquid ammonia (50 mL) and catalytic amount of ferric nitrate, freshly cut fine lithium metal pieces (5.2 g) were added, and the mixture was stirred at –33 ^{o}C four 30 minutes. A solution of **8** (6.3 g, 27.5 mmol) in THF (15 mL) was added drop wise and the reaction mixture was stirred for 2 h, and the reacton was quenched by using solid ammonium chloride and ammonia was allowed to evaporate. The residue was dissolved in diethylether and filtered. The filtrate was dried over Na_2SO_4 and crude was purified by column chromatography to give compound **9** as a liquid in 93% of yield (4.6 g).

^{1}H NMR (200 MHz, $CDCl_3$)

δ 5.80 (d, *J* = 9.8, 2H), 4.37 (br, s, 1H), 2.62 (t, *J* = 10.2, 2H), 2.20 (s, 3H, -CH_3), 1.61-1.83 (br, m, 5H), 1.43 (br, s, 1H).

IR (neat)

3453, 2926, 1635, 1219,772 cm-^{1}.

Mass

m/z 178 (M^+).

[α] ^{D}

-0.85^o (C=1.15 $CHCl_3$).

(s)-2-(4-benzyloxy) hex-5-ynyl)-5-methylfuran

A well-stirred suspension of freshly activated NaH (60% w/v dispersion in mineral oil) in anhydrous THF (0.78 g, 65.5 mmol), a solution of compound (**9**) (4.60 g, 25.1 mmol) in dry THF (15 mL) was added drop wise at 0 ^{o}C. After 30 minutes, benzyl bromide (2.80 g, 16.3 mmol) was added and the reaction mixture was brought to room temperature and stirred for 8 h. The solid ice pieces were added to quench the reaction and the THF layer was separated by aqueous layer and was extracted with ether. The combined organic layers were washed with water, brine and dried over Na_2SO_4. After removing the volatiles under reduced pressure, crude benzyl ether was purified by column chromatography with 10% EtOAc in hexane as an eluent to furnish **10** (3.5 g, 84% of yield) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.21 (s, 5H), 5.70 (s, 2H), 4.78 (d, *J* = 17.4 Hz, 1H), 4.40 (d, *J* = 17.42 Hz, 1H), 4.01 (s, 1H), 2.50 (s, 2H), 2.21 (s, 3H, -CH_3), 1.77-1.83 (m, 3H), 1.20 –1.30 (s, 2H).

IR (neat)

3043, 2943, 2276, 1397, 780 cm^{-1}.

Mass

m/z 291(M^+).

[α] ^{D}

-21.96^o (C=1.3 $CHCl_3$).

(S)-Ethyl-4-(*tert*-butyldimethylsilyloxy)-7-(5-methylfuran-2-yl) hept-2-ynoate

The solution of compound **10** (3.50 g, 12 mmol) in dry THF at –78 ^{o}C, n-butyl lithium [0.98 g (10.2 mL), 8.9 mmol] was added drop wise and stirred 2 h. The reaction mixture was warmed to –50 ^{o}C, and to this solution slowly ethyl chloroformate (1.4 g, 13.6 mmol) was added. The reaction mixture was allowed to stir for 1 h till the reaction mixture turns to orange red colour. The product was extracted with ethyl acetate and washed with water, brine and dried over Na_2SO_4, concentrated under vacuum. The crude product was purified by column chromatography to afford compound (**11**) as a liquid with 96% of yield (3.06 g).

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.20 (s, 5H), 5.80 (s, 2H), 4.80 (d, *J* = 15.6 Hz, 1H), 4.40 (d, *J* = 15.6 Hz, 1H), 4.20, (q, $J_{1,2}$ = 10.9 Hz, $J_{1,3}$ = 19.8 Hz, 2H), 4.18 (s, 1H), 2.60 (t, J = 6.2 Hz, 2H), 2.20 (s, 3H, -CH3), 1.64-1.90 (m, 3H), 1.30 (d, *J* = 9.3 Hz, 4H).

IR (neat)

3030, 2940, 1750, 1635, 1389, 772 cm^{-1}.

Mass (LCMSD)

m/z 340 (M^+).

[α] ^{D}

-7.43^o (C=1.15 $CHCl_3$).

^{13}CNMR (200 MHz, $CDCl_3$)

δ 158.0, 154.5, 151.5, 138.3, 130.2, 130.0, 130.1, 128.9, 106.1, 106.3, 86.5, 78.0, 72.0, 64.9, 52.0, 31.1, 27.0, 18.5, 13.7, 13.5.

(*S*, Z)-Ethyl-4-(*tert*-butyldimethylsilyoxy)-7-(5-methylfuran-2-yl)hept-2-enoate

To a solution of compound (**11**) (3.0 g, 23.1 mmol) in ethanol (20 mL) at room temperature was added catalytic amount of Lindlars catalyst (1/20) in one portion and was stirred at room temperature for 6 h under hydrogen atmosphere. The crude product was passed through celite-bed, washed with ethanol (2-3 times). The filtrate was concentrated. The product was purified by column chromatography to yield 90% the compound **12** (7.5 g) as a colourless liquid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.30 (s, 5H), 6.21 (s, d, s, *J* =11.70 Hz,[1,3 Coupling] 1H), 5.85 (d, *J* = 11.70 Hz, 1H), 5.75 (s, 2H), 5.15 (s, 1H), 4.50 (d, *J* = 12.4 Hz, 1H), 4.40 (d, *J* = 12.4 Hz, 1H), 4.25 (q, $J_{1,2}$ = 9.9 Hz, $J_{1,3}$ = 18.3 Hz,1H), 2.56 (t, *J* = 10.4 Hz, 2H), 2.20 (s, 3H, -CH_3), 1.64-1.85 (m, 3H), 1.21-1.53 (m, 5H).

IR (neat)

3045, 2926, 1764, 1636, 1361, 776 cm^{-1}.

Mass

m/z 343 (M+1).

$[\alpha]^{D}$

12.78^{o} (C=1.15 $CHCl_3$).

Diels-Alder Adduct

Compound (**12**) was subjected to Diels-Alder reaction under dry condition in a sealed tube with higher dilution of toluene at 190 ^{o}C in sand bath and stirred for more than 12 days. The solvent was concentrated under vacuum and the crude product was purified by column chromatography to yield compound **13** as a colorless liquid (20% yield).

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.28 (s, 5H), 5.92 (q, J1,2 = 5.3 Hz, J1,3 = 10.7 Hz, 1H), 5.42 (d, J = 8.0 Hz, 1H), 5.21 (s, 1H), 4.58 (d, J = 10.7 Hz, 1H), 3.62 (d, J = 10.7 Hz, 1H), 4.16 (q, J 1,2 = 5.3 Hz, J 1,3 = 16.0 Hz, 2H), 2.40-20 (m, 2H), 2.02-1.90 (m, 2H), 1.80-1.12 (m, 10H).IR

IR (Neat)

3056, 1756, 1632, 1364, 1156, 765 cm^{-1}.

Mass

m/z 343 (M+1).

Compounds 14a and 14b

The H_3Al was prepared from a solution of 76.62 mg (6.14 mmol) of $LiAlH_4$ in 5 mL of ether, mixed with a solution of 63.15 mg (7.60 mmol) of $AlCl_3$ in 5 mL of ether at –50 ^{o}C. The resulting mixture of hydrated solution was stirred at r.t for 15 minutes. To this mixture compound **13** was added slowly at 0 ^{o}C. The reaction mixture was allowed to warm to room temperature for 30 minutes. The reaction mixture was cooled to 0 ^{o}C and quenched with saturated sodium sulphate by drop wise addition. The precipitated solid was filtered and the filtrate was dried over sodium sulphate and concentrated under vacuum. The crude product was purified by column chromatography to get **14a** and **14b** as a colorless liquid, 13 mg in 65 % of yield. .

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.26 (s, 5H), 6.18 (d, t, d, J = 2.6 Hz, 1H), 5.84 (d, J = 8.3 Hz, 1H), 5.44 (d, J = 10.0 Hz, 1H), 4.36 (d, J = 8.3 Hz,1H), 4.12 (q, J 1,2 = 6.6 Hz, J 1,3 = 16.0 Hz, 2H), 2.38- 2.20 (m, 2H), 2.01-1.82 (m,2H), 1.71-1.18 (m, 13H).

IR (neat)

3456, 3043, 1750, 1643,756 cm^{-1}.

Mass

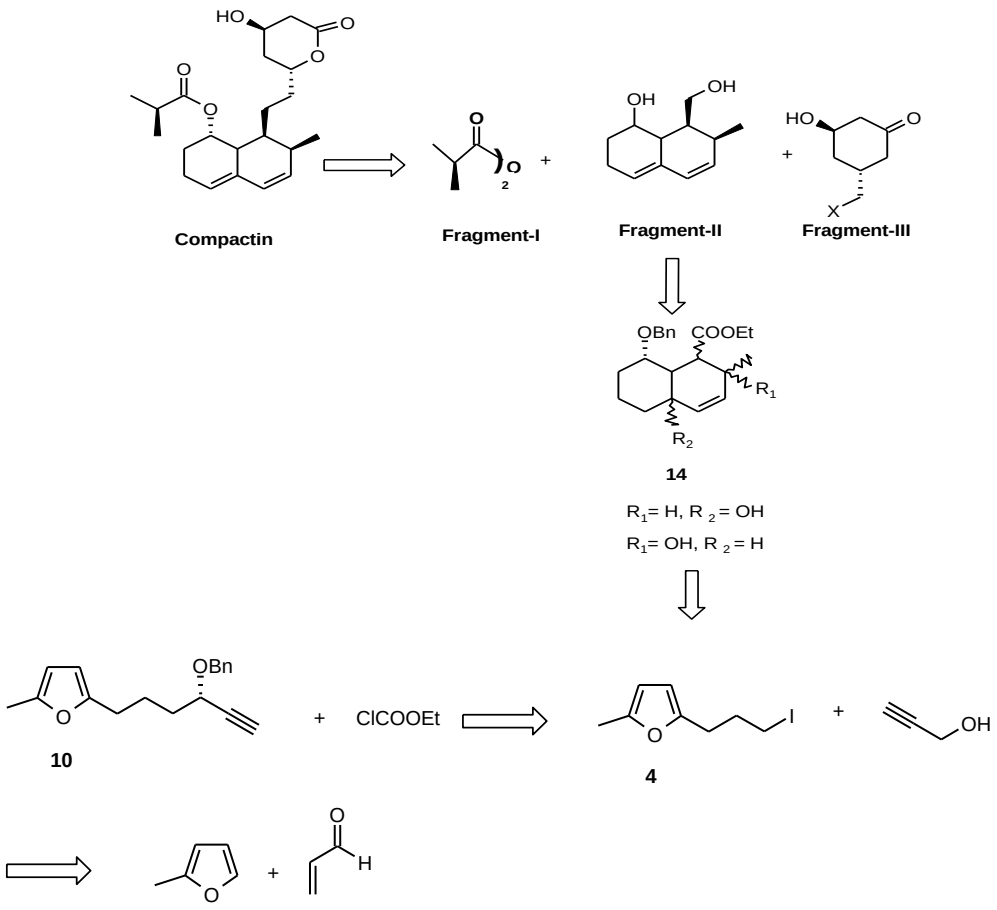
m/z 344.9 (M^{+}1).

RESULTS AND DISSCUTION

The retrosynthetic analysis of compactin revealed three main fragments I, II and III. Fragment II can be obtained from **14a** which intern can be obtained from **12** by intramolecular Diel's-Alder reaction.

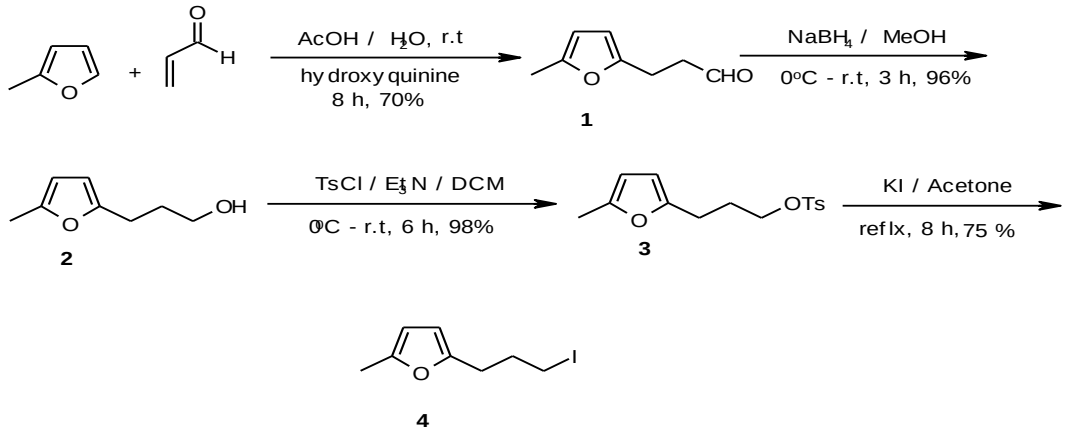
Retro synthetic strategy

Scheme 1



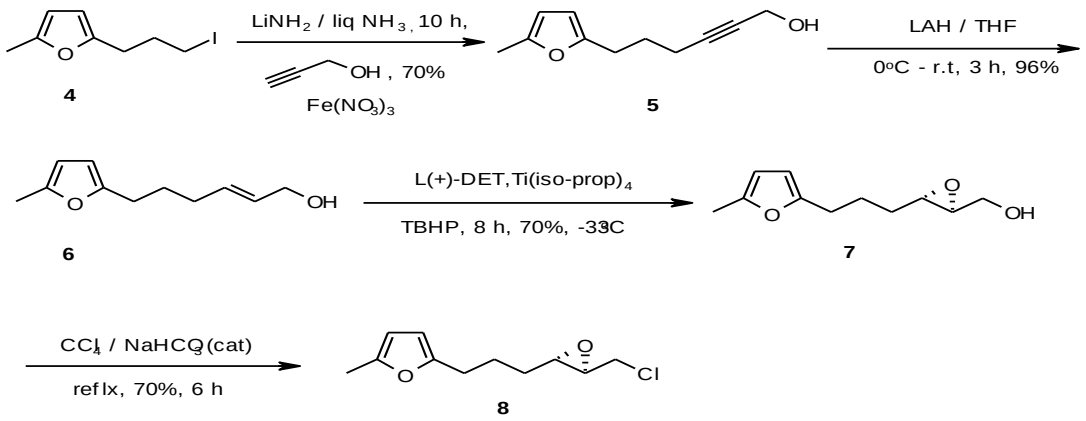
A freshly distilled 2-methyl furan was treated with 1.2 equivalent of acrolein in acidified water (1ml of ACOH in water). A little amount of hydroxyquinine was added to prevent polymerization of acrolein and stirred at ambient temperature for 8 h, yielding 70% of 3-(5-methylfuran-2-yl) propanal **1**.

Scheme 2



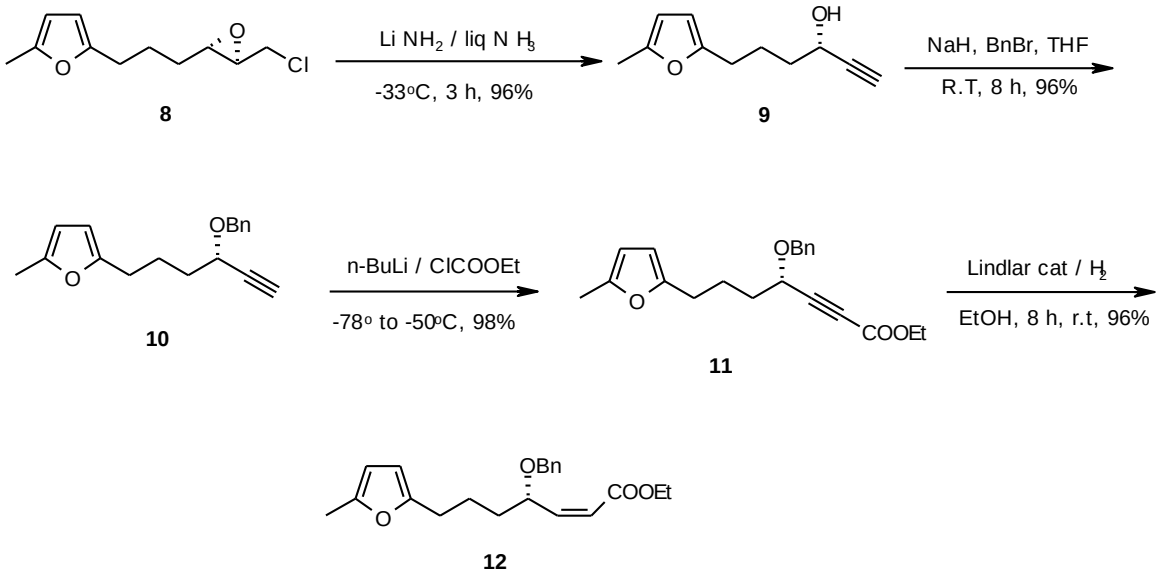
The reduction of 3-(5-methylfuran-2-yl) propanal **1** to reduced product **2** was achieved by stirring with $NaBH_4$ in anhydrous methanol at 0 ^oC - r.t for 3 h yielding 96% of alcohol **1**. The compound 3-(5-methylfuran-2-yl) propan-1-ol was transformed to tosyl protected precursor using standard condition by adding 1.2 equivalent of triethyl amine and tosylchloride in dichloromethane at 0 ^oC to room temperature for 6 h yielding 98% of **3**. Exposure of compound **3** to excess of KI in acetone at reflux condition smoothly afforded the desired iodo compound 2-(3-iodopropyl)-5-methylfuran **4** in 8 h in 85% yield.

Scheme 3



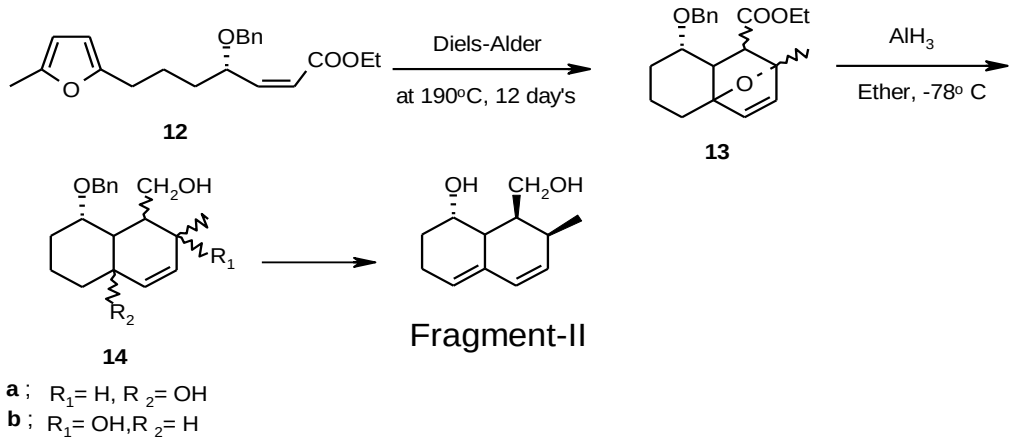
Propargyl alcohol was subjected to reaction with lithium amide in liq. NH_3 and treated with compound **4** in liquid ammonia at –33 ^oC to give compound **5**, 6-(5-methylfuran-2-yl) hex-2-yn-1-ol in 10 h in 70% yield. Propargylic alcohol **5** was reduced with 1.2 equivalent of $LiAlH_4$ in THF to offer *trans* allyl alcohol at room temperature yielding 96% of compound (*E*)-6-(5-methylfuran-2-yl) hex-2-en-1-ol. Treatment of **6** with L- (+)-DET, titanium tetraisopropoxide and TBHP in anhydrous CH_2Cl_2 at –33 ^oC gave the epoxy alcohol[9] **7** in 78% yield. The epoxy alcohol **7** was converted to epoxy chloride by using triphenyl phosphine and $NaHCO_3$ in reflux with CCl_4 for 6 h.

Scheme 4



The key step was the execution of our earlier approach for the preparation of the chiral propargyl alcohol from chiral 2,3-epoxy chlorides using LDA or $LiNH_2$ in liquid ammonia[10], wherein chiral 2,3-epoxy chlorides are subjected to the base induced double bond elimination using $LiNH_2$ or LDA to produce chiral proporgyl alcohols. Accordingly 8 was subjected to our reaction conditions, in liquid ammonia using lithium amide to get the chiral propargyl alcohol at –33 ^oC yielding 96% of 9 ((S)-6-(5-methylfuran-2-yl) hex-1-yn-3-ol) in 3 h. The secondary hydroxyl functionality of compound **9** was selectively protected as its benzyl ether using 2 equivalent of sodium hydride (60% w/v dispersion of oil) and benzyl bromide in anhydrous THF at reflux temperature to afford 10 in 8 h with 96% yield. The benzyl-protected ether 10 was lithiated-using n-BuLi at –78 ^oC followed by addition of 1.2 equivalent of ethyl chloroformate at –50 ^oC to give the corresponding esterified compound[11] yielding 90%. The compound 11 was subjected to Lindlar's hydrogenation reaction in ethanol to give corresponding *cis*-alkene 12 in 90% of yield.

Scheme 5

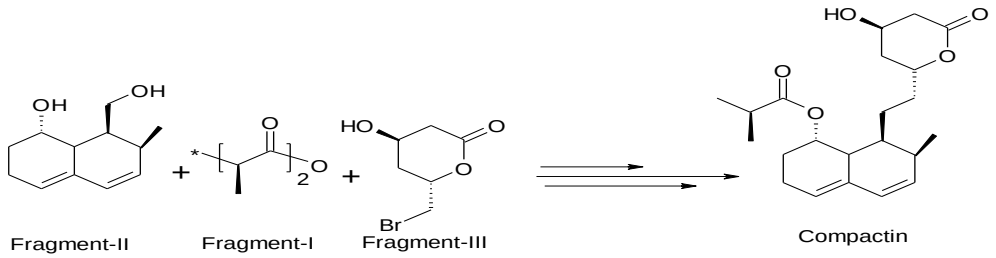


Compound **12** on intramoleculer Diels-Alder reaction gave Diel's-Alder adduct at 190^oC in toluene for 12 days, yielding bicyclic compound **13** approximately 20% at higher dilution. The resulting dihydrofuran adduct was accessible by AlH_3 in ether at –78 ^oC to get the product intermediate[12] **14a** or **14b**.

CONCLUSION

Further 14a or 14b subjected to debenzylation to form Fragment-II this bicyclic diol coupled with Fragment-I which is available commercially and Fragment-III which is prepared in our lab. The final compactin was obtained after five stapes.

Scheme 6



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