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Research Article

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Novel synthesis of Ticagrelor, an anti-thrombotic agent

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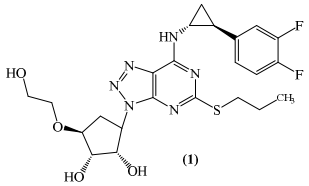
ABSTRACT

Ticagrelor is a known orally active compounds act as $P2Y_{12}$ (formerly known as P2T receptor) receptor antagonists [1] and they are indicated for use in therapy as inhibitors of platelet activation, aggregation and degranulation, promoters of platelet disaggregation, and anti-thrombotic agents [2]. The present work describes a novel process of Ticagrelor and its novel intermediate synthesis, characterization and control of related substances, thereby providing a commercial method to synthesize substantially pure Ticagrelor.

Keywords: Ticagrelor, Antithrombotic agent

INTRODUCTION

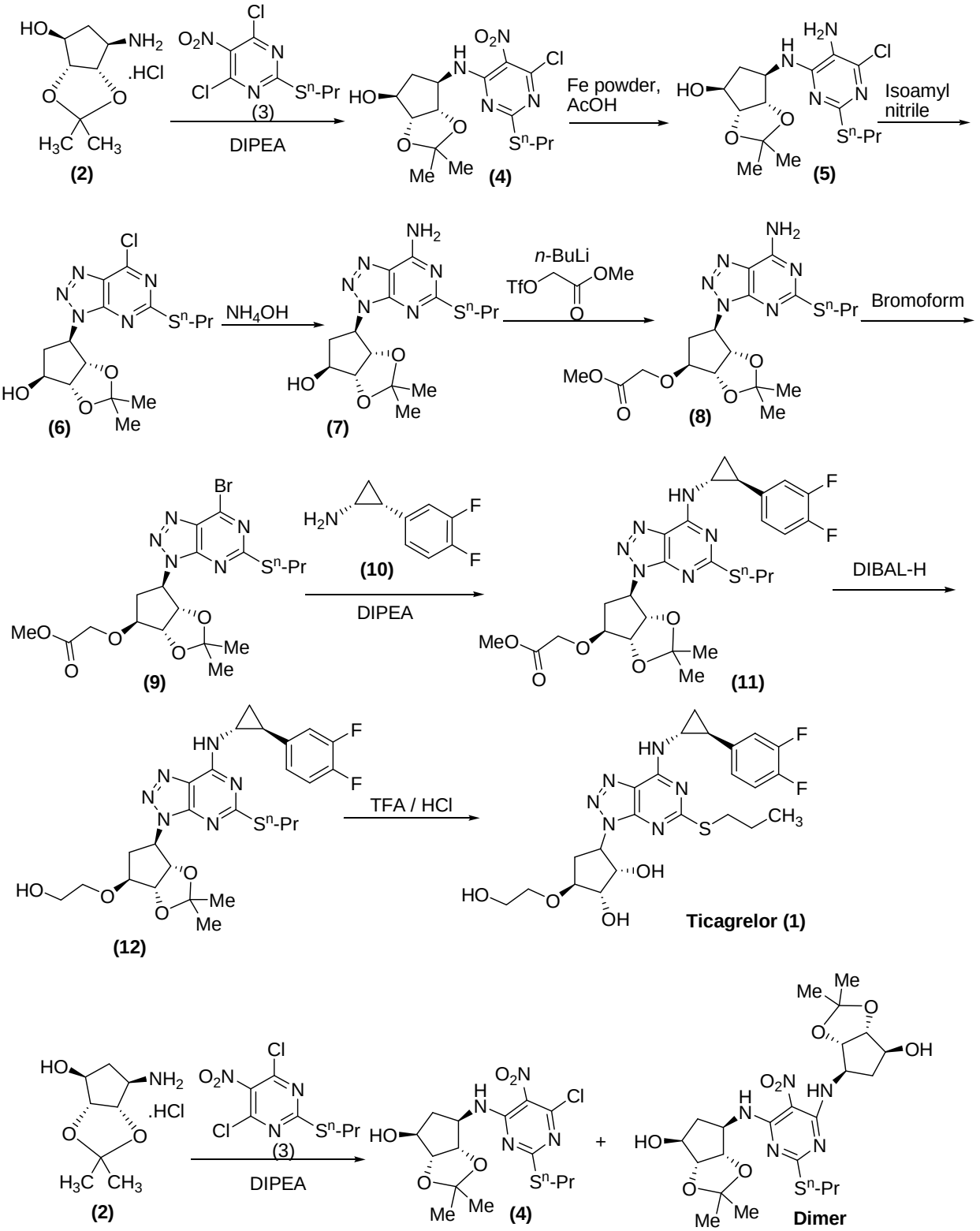
Ticagrelor (**1**) acts as an adenosine uptake inhibitor, a platelet aggregation inhibitor, a $P2Y_{12}$ purinoceptor antagonist, and a coagulation inhibitor. It is indicated for the treatment of thrombosis, angina, ischemic heart diseases, and coronary artery diseases [3]. Ticagrelor is the first reversibly binding oral adenosine diphosphate (ADP) receptor antagonist and is chemically distinct from thienopyridine compounds like Clopidogril. It selectively inhibits $P2Y_{12}$, a key target receptor for ADP. ADP receptor blockade inhibits the action of platelets in the blood, reducing recurrent thrombotic events. The drug has shown a statistically significant primary efficacy against the widely prescribed Clopidogril [4] (PLAVIX) in the prevention of cardiovascular (CV) events including myocardial infarction (heart attacks), stroke and cardiovascular death in patients with acute coronary syndrome (ACS). Ticagrelor is represented by the following structural formula **(1)**:



(1)

According to the literature (Scheme-1), the large scale synthesis of Ticagrelor (**1**) (AZD6140) [3] is begin with by condensation of **3** with **2** in the presence of DIPEA in THF to produce **4**. The obtained **4** on reduction with iron powder in acetic acid provides**5**, which is then reacted with isoamyl nitrite in acetonitrile to produce **6**. The resulting triazolo[4,5-d]-pyrimidine compound **6** is reacted with ammonia in THF to produce **7**, which is then reacted with a solution of trifluoromethanesulfonyloxy-acetic acid methyl ester in THF using *n*-butyllithium as a base to produce **8**, followed by bromination using Bromoform to produce **9**. The resulting bromo-compound **9** is then reacted with (1*R*-trans)-2-(3,4-difluorophenyl)cyclopropanamine **10** in the presence of DIPEA and DCM to produce **11**, followed by

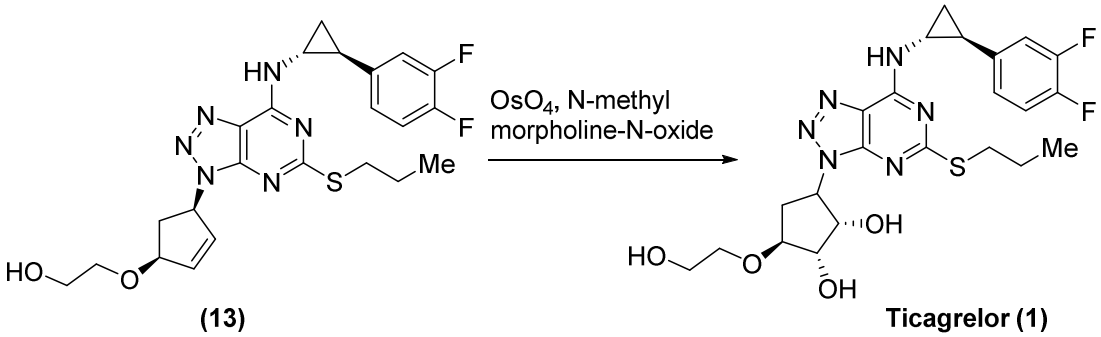
reaction with DIBAL-H in THF to produce **12**, which is then treated with Trifluoroacetic acid and water to produce Ticagrelor (**1**).



Scheme-1. Reported route of synthesis for Ticagrelor (1)

In the existing route (Scheme-1) of Ticagrelor synthesis have disadvantages such as no control on dimer impurity formation (during condensation of **2**&**3**,displacement of both chloro groups with compound **3** and leads to dimer impurity, scheme-1). Chloro group of **6** converted to amino group in **7** and further converted it back to bromo derivative in **9**. This inter-conversion increases the number of steps and which affect the overall yield of the process.

According to the literature (Scheme-2)[5], Ticagrelor is prepared by Dihydroxylation of Cyclopentyl moiety **13** using Osmium tetroxide 2.5% solution in t-butanol in the presence of acetone. Usage of Osmium tetroxide in the last stage has most likely chances of its contamination in API. Osmium tetroxide is highly poisonous [6], even at low exposure levels [7], even the effluent generated is highly toxic and must be handled with appropriate precautions.



(13) **Ticagrelor (1)**

Scheme-2. Dihydroxylation of 13

EXPERIMENTAL SECTION

The IR spectra were recorded using a Perkin-Elmer spectrum one FT-IR spectrometer instrument by using 1% potassium bromide pellet technique. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 300 MHz & 75 MHz respectively on Bruker 300 MHz Advance NMR spectrometer using Tetramethylsilane as the internal standard. Mass spectra (MS) were recorded on Agilent 1100 Series LC-MSD-TRAP-SL instrument.

Reactions were monitored by thin layer chromatography on 0.2 mm silica gel 60 F_{254} (Merck) plates using UV light (254 and 366 nm) for detection. Common reagent-grade chemicals are commercially available and were used without further purification.

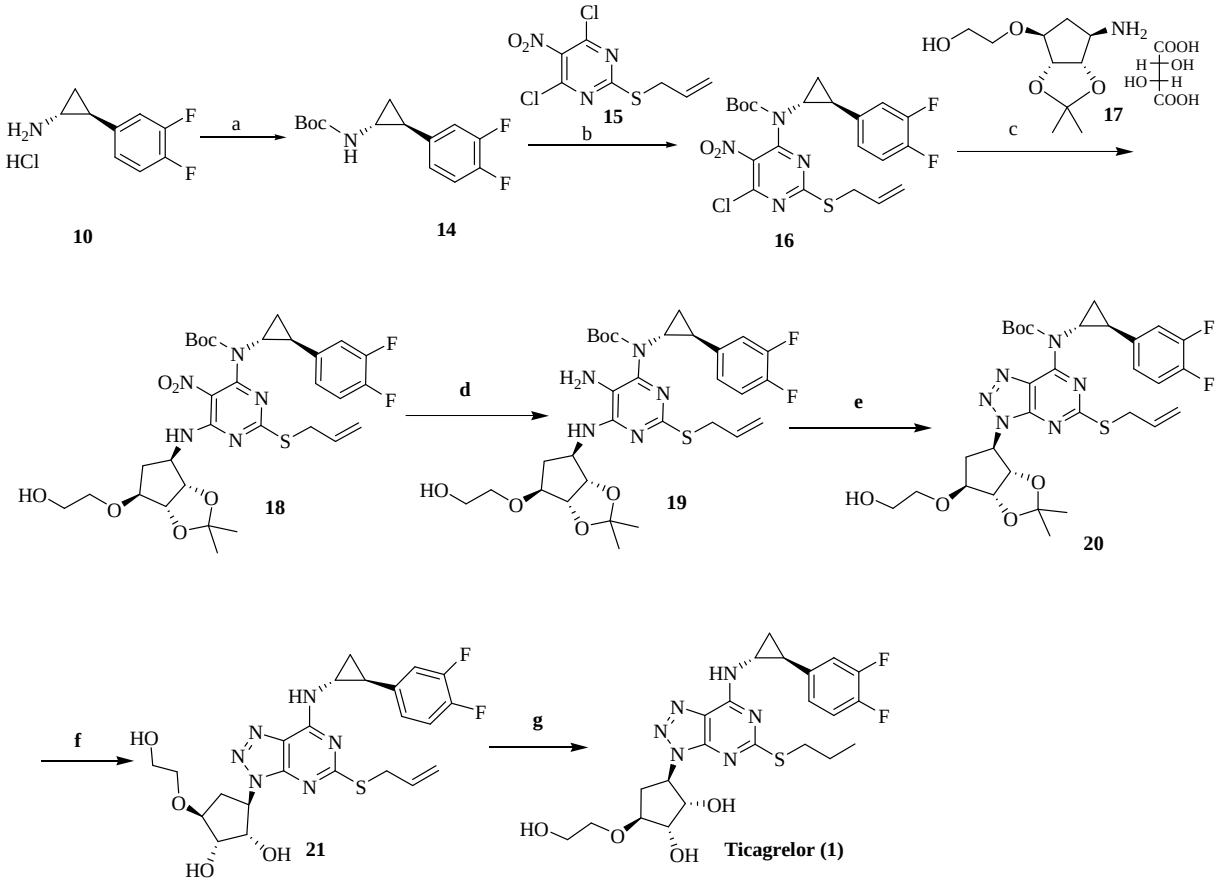
In the present work, the synthesis of **1** is begun with the N-BOC protected cyclopropyl amine**14**(Scheme-3). This route of synthesis involved novel intermediates. The compound **10** can be prepared as per the reported literature [2, 8,9]. The compound **10** is protected by Boc-anhydride to get Boc-protected compound **14**, this compound was treated with NaH to generate anion which was further reacted with dichloro-nitro compound **15** in the presence of THF solvent to provide the coupled product **16**. The obtained **16**was reacted with **17** in the presence of TEA as a base and Ethyl acetate solvent and obtained **18**. The compound **17**wasknown in the literature [2, 9, 10] & was prepared as per the reported literature. Reduction of **18**was carried out using sodium dithionite and Sodium carbonate in acetone, provided the **19**. This was treated with $NaNO_2$ in the presence of Acetic acid, Toluene mixture and obtained the cyclized product **20**. Deprotection of Acetal and Boc group of**20** was carried out using HCl in the presence of Methanol solvent and isolated crystalline solid material of **21**from Ethyl acetate and hexanes mixture. Finally **21** was reduced using hydrazine hydrate and Sodium periodate and final isolation from mixture of Ethyl acetate and hexanes solvents provided pure Ticagrelor (**1**) with the purity above 99.8%and overall yield of 52.7% from **10**.

Compound **15** was synthesized from Diethyl malonate in four steps (Scheme-4). Diethyl malonate**22** was nitrated with Nitric acid to get Nitro compound **23**, which was reacted with Thiourea to get pyrimidine compound **24**, which was reacted with allyl bromide to get **25**. This compound is treated with phosphorous oxychloride to get Dichloro-nitro-pyrimidine compound **15.**

5-nitro-2-sulfanylpyrimidine-4, 6-diol (24)

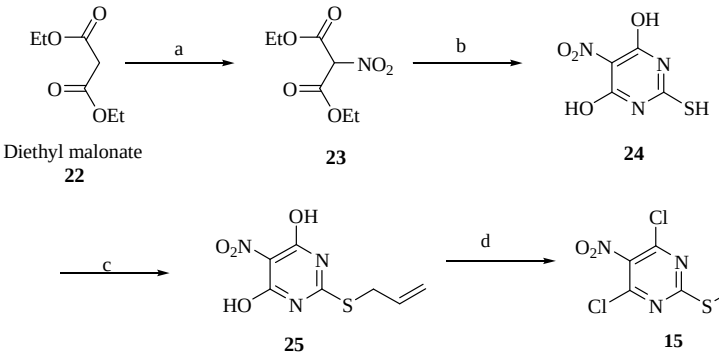
Diethyl malonate (100.0 g, 0.62 mol) was taken into flask and cooled to 10-15°C, fuming nitric acid (137.0 g, 2.17 mol) was added slowly. Temperature was adjusted to 15-20°C. After completion of the reaction, the reaction mass was quenched to mixture of water (400 ml) and toluene (300 ml). Aqueous layer was extracted with toluene (300 ml). Organic layers was combined and washed with water (500 ml) followed by 5% urea solution (500 ml) and compound **23** was extracted to aqueous layer using sodium carbonate solution (600 ml). pH of the aqueous layer was adjusted to 1.5 -2.5 with HCl and the compound **23** was extracted with Toluene (500 ml). Organic layer was washed with by 5% urea solution (250 ml) followed by water (250 ml), then the organic layer was dried on sodium sulfate (100.0 g). In another flask sodium methoxide (78.0 g, 1.44 mol), Toluene (180 ml), Thiourea (50.0 g, 0.657 mol) was added followed by above sodium sulfate dried Toluene layer. Reaction mass was heated to 50-60°C& maintained for 3 hrs. After completion of reaction water (270 ml) was added to the reaction mass and pH of the reaction mass was adjusted to 2.0-3.0 with HCl. Reaction mass was cooled to room temperature and stirred for 2 hrs, filtered the reaction mass and washed with water: methanol (1:1, 200 ml) mixture and dried to get 105 g of **28**,89%

yield. Melting range 110-124°C;[1]H NMR (DMSO-d_6,300 MHz) (δ, ppm): 11.15 (bs, 3H);[13]C NMR (DMSO-d_6,75 MHz) (δ, ppm): 115.2, 157, 174.7; Mass (m/z): 188 (M-H).



Scheme-3. Reagents and conditions:(a) BOC-anhydride, MDC, Hexanes, $NaHCO_3$, 25^{-30}°C; (b) NaH, THF, Hexanes, -20°C; (c) EtOAc, TEA, Hexanes, 50^{-55}°C; (d) Acetone, Na_2CO_3, $Na_2S_2O_4$, EtOAc, IPA, 30-35°C; (e) Toluene, $NaNO_2$, AcOH, Na_2CO_3 10^{-15}°C; (f) MeOH, HCl, Na_2CO_3, EtOAc, Hexanes, 10^{-15}°C; (g) THF, EtOH, Hydrazine hydrate, $NaIO_4$, EtOAc, Hexanes, 50^{-55}°C.

Scheme-3. Synthesis of Ticagrelor (1)



Scheme-4. Reagents and conditions: (a) Fuming HNO_3, Toluene, Urea, Na_2CO_3, 10^{-20}°C; (b) Thiourea, NaOMe, HCl, MeOH, 50^{-60}°C; (c) NaOH, Allylbromide, HCl, Acetone (d) $POCl_3$, DIPEA, Toluene, 80^{-90}°C.

Scheme-4. Synthesis of15

5-nitro-2-allylthiopyrimidine-4,6-diol (25).

Sodium hydroxide (75.0 g, 1.87 mol) was dissolved in water (750 ml).Compound **24** (100.0 g, 0.529 mol) was added and stirred till clear solution. Allyl bromide (67.0 g, 0.55 mol) was added slowly drop wise to the reaction mass at room temperature and maintained for 2 hrs. After completion of the reaction, pH of reaction mass was adjusted to 4.5-5.5 with HCl. Acetone (100 ml) was added to the reaction mass and stirred for 4-6 hrs. Product was filtered and washed with acetone: water mixture (1:1) (100 ml) and dried to get 105 g of**25**, 86.8% yield. Melting

range 80-101°C;[1]H NMR (DMSO-d_6,300 MHz) (δ, ppm): 3.69(d,2H,*J*=6.9Hz), 5.81-5.94(m, 1H), 5.10 (d, 1H, *J*=10.2 Hz), 5.24-5.30(dd, 1H,*J*=16.8 Hz, 1.2 Hz), 11.21 (bs, 2H); [13]C NMR (DMSO-d_6,75 MHz) (δ, ppm):32.0, 117.8, 118.2, 133.5, 158.5, 163.7; Mass (m/z): 230 (M+H).

4,6-dichloro-5-nitro-2-(prop-2-en-1-ylsulfanyl)pyrimidine (15).

To a stirred solution of Toluene (400 ml) and compound **25** (100.0 g, 0.44 mol), phosphorous oxychloride (350.0 g, 2.3 mol) was added followed by Diisopropylethylamine (115.0 g, 0.89 mol).The reaction mixture was heated up to 80-90 °C and maintained for 4 hr. after completion of the reaction, reaction mass was distilled out under vacuum followed by stripping with Toluene (100 ml), Toluene (500 ml) was added to the reaction mass, followed by addition of ice-water (600 ml) at 10-20 °C. Layers were separated and aqueous layer was extracted with Toluene (200 ml). Both Toluene layers were mixed and washed with 5% Sodium bicarbonate solution (400 ml), followed by 20% sodium chloride solution (400 ml). Organic layer was stirred with silica (80.0 g) followed by charcoalization with activated charcoal (5.0 g) at 50-55 °C. Organic layer was then concentrated under reduced pressure at below 65 °C to get lemon colored residue 104 g of **15**, yield 89.6%. [1]HNMR(DMSO-d_6,300 MHz) (δ, ppm): 3.85 (dd, 2H, *J* = 6.9, 0.9 Hz), 5.23 (dd, 1H,*J* = 9.9, 0.9 Hz), 5.39 (dd, 1H,*J* = 16.8, 1.2 Hz), 5.85-5.98 (m, 1H); Mass (m/z): 266 (M+)

***tert*-butyl [(1*R*, 2*S*)-2-(3,4-difluorophenyl)cyclopropyl] carbamate (14).**

To a stirred solution of water (1000 ml), (1*R*, 2*S*)-2-(3,4-difluorophenyl)cyclopropanamine hydrochloride, i.e. compound **10** (100.0 g, 0.48 mol) was added and dissolved completely. To this solution sodium bicarbonate (100.0 g, 1.19 mol), dichloromethane (700 ml) was added followed by slow addition of Boc-anhydride (127.0 g, 0.58 mol) at 25-30 °C and maintained for 60 min. After completion of the reaction, layers were separated and aqueous layer was extracted with dichloromethane (200 ml). Dichloromethane layers were mixed and washed with 15%Sodium chloride solution (300 ml). Organic layer was stripped off at below 45 °C with hexanes (200 ml) to get residue. Hexanes (700 ml) was added to the residue and heated up to 60-70 °C and maintained for 30 min. Reaction mass was then cooled to 25-35 °C and maintained for 60 min, further it was cooled to 10-15 °C and maintained for 2 hrs. Slurry was filtered and washed with chilled hexanes and dried under vacuum at 45-50 °C to get 128 g of **14**, yield 97.8%. [1]HNMR(DMSO-d_6,300 MHz) (δ, ppm): 1.38 (s, 9H), 2.59 (bs, 1H), 1.08-1.16 (m, 2H), 1.88 – 1.94 (m, 1H), 6.96 (bs, 1H), 7.11-7.34 (m, 3H);[13]CNMR (DMSO-d_6,75 MHz) (δ, ppm):15.27, 23.49, 28.14, 33.23, 77.86, 114.62 (d, *J* = 17.2 Hz), 116.94, 155.95, 122.62-122.73 (dd, *J* = 5.7, 3.0Hz), 139.47-139.60 (dd, *J* = 6.1, 3.5 Hz), 146.92-149.31 (dd, *J* = 241.2, 12.6 Hz), 147.59-151.00 (dd, *J* = 243.0, 12.6 Hz); Mass(m/z): 292 (M+Na).

***tert*-butyl[6-chloro-5-nitro-2-(prop-2-en-1-ylsulfanyl)pyrimidin-4-yl][(1*R*,2*S*)-2-(3,4-difluorophenyl) cyclopropyl]carbamate (16)**.

To a Sodium hydride (25 g, 0.63mol), Tetrahydrofuran (500 ml) was added under nitrogen atmosphere and cooled to -10 °C. Solution of compound **14** [(96.0 g, 0.36mol) was dissolved in Tetrahydrofuran (300 ml)] and was added slowly to the pre-cooled sodium hydride solution at -7 to -13 °C, reaction mass temperature was adjusted to 20 °C and maintained for 120 min. In another flask Dichloro-nitro-compound **15** (100.0 g, 0.37mol) was dissolved in Tetrahydrofuran (500 ml) under nitrogen atmosphere and cooled to -20 °C. Above prepared solution of Sodium hydride was added to this solution by maintaining temperature at -10 to -20 °C, after completion of the reaction temperature was raised and 20% Sodium chloride solution (500 ml) was added and separated the layers. Organic layer was concentrated by vacuum distillation and stripped off with hexanes (200 ml) to get residue. Hexanes (1000 ml) was charged to the residue and stirred at room temperature for 3-4 hr. The obtained slurry was filtered and washed with hexanes (100 ml). Filtrate was then concentrated under vacuum at below 55 °C to get 182 g residue of **16**, yield 98.4%. [1]HNMR(DMSO-d_6,300 MHz) (δ, ppm): 1.24-1.40 (m, 2H), 1.43 (s, 9H), 2.21-2.28 (m, 1H), 3.13-3.18 (m, 1H), 3.68-3.83 (m, 1H), 5.18 (d, 1H,*J* = 10.2 Hz), 5.33 (d, 2H,*J* = 18.0 Hz), 5.82-5.96 (m, 1H), 6.92-7.13(m, 1H);Mass (m/z): 498 (M+).

***tert*-butyl [(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl][6-{[(3a*S*,4*R*,6*S*,6a*R*)-6-(2-hydroxyethoxy)-2,2-dimethyl tetrahydro-3a*H*-cyclopenta[4,5-*d*][1,3]dioxol-4-yl]amino}-5-nitro-2-(prop-2-en-1-ylsulfanyl)pyrimidin-4-yl] carbamate (18).**

Residue of compound **16** (182g) was dissolved in Ethyl acetate (600 ml), 2-{[(3a*R*,4*S*,6*R*,6a*S*)-6-amino-2,2-dimethyltetrahydro-3a*H*-cyclopenta[4,5-*d*][1,3]dioxol-4-yl]oxy}ethanol, L-tartarate salt i.e. compound **17** (105 g, 0.286 mol) was added to it followed by addition of Triethylamine (55.0 g, 0.544 mol), reaction mass was heated up to 50-55 °C and maintained for 90-120 min. After completion of reaction, reaction mass was cooled to room temperature and water (300 ml) was added. Layers were separated and organic layer was washed with 20% Sodium chloride solution (300 ml), then subjected to charcoal treatment with activated charcoal (5.0 g), followed by distillation under vacuum to get residue. Ethyl acetate (50 ml) and hexanes (1500 ml) were added to residue and heated to 50-55 °C, then cooled to room temperature and maintained for 4-6 hrs, filtered the solid material and dried to get 205 g of compound **18**, yield 82.8%. Melting range 109.4-114 °C;[1]HNMR (DMSO-d_6,300 MHz) (δ, ppm): 1.22-1.50 (m, 6H), 1.22-1.50 (m, 9H), 1.22-1.50 (m, 2H), 1.89-1.93 (m, 1H), 2.17-2.27 (m, 2H), 3.09-3.13 (m,1H),

3.57-3.59 (m, 4H), 3.74 (d, 2H,*J* = 6.6 Hz), 3.93 (d, 1H), 4.52-4.65 (m, 4H), 5.10 (d, 1H,*J* = 9.9 Hz), 5.31 (d, 1H,*J* = 16.8 Hz), 5.86-6.00 (m, 1H), 7.08-7.37 (m, 3H), 8.47(d, 1H,*J* = 8.1 Hz);^{13}CNMR (DMSO-d_6,75 MHz) (δ, ppm): 17.74, 23.72, 26.03, 25.64, 27.46, 32.57, 33.47, 38.85, 56.64, 59.99, 70.82, 82.31, 82.37, 84.42, 109.75, 115.28(d, *J* = 17.3 Hz), 116.93 (d, *J* = 16.9 Hz), 117.93, 121.12, 133.57, 151.88, 153.29, 155.74, 171.76, 123.12-123.25(dd, *J* = 6.2, 3.3 Hz), 138.18-138.29 (dd, *J* = 6.0, 3.5 Hz), 146.22-149.61 (dd, *J* = 242.1, 12.5 Hz), 147.53-150.94 (dd, *J* = 243.1, 12.6 Hz); Mass (m/z): 680 (M+1).

***tert*-butyl [5-amino-6-{[(3a*S*,4*R*,6*S*,6a*R*)-6-(2-hydroxyethoxy)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[4,5-*d*] [1,3]dioxol-4-yl]amino}-2-(prop-2-en-1-ylsulfanyl)pyrimidin-4-yl][(1*R*,2*S*)-2-(3,4-difluorophenyl) cyclopropyl] carbamate (19).**

Compound **18** (100 g, 0.147 mol) was dissolved in Acetone (500 ml). Sodium carbonate solution (75 g dissolved in water 500 ml) was added to the above solution at room temperature. Sodium dithionite (125 g, 0.718 mol) was added in lot wise to the reaction mass at room temperature and stirred for 2 hrs after completion of reaction Ethyl acetate (1000 ml) and water (1000 ml) was added to the reaction mass and separated the layers. Organic layer was washed with 20% sodium chloride solution (400 ml). Organic layer was then concentrated under vacuum at below 55 °C to get residue. The residue was stripped off with IPA (50 ml).To the residue, IPA (125 ml) was charged and heated up to 60-65 °C for 60 min, subsequently cooled to room temperature, it was further cooled to 0-5 °C and maintained for 2-3 hrs and filtered. The material was dried at below 55 °C to get 86 g of compound **19**, yield 90.05%. Melting range 176.2 – 180.4 °C;^{1}HNMR (DMSO-d_6,300 MHz) (δ, ppm): 1.01-1.19 (m, 2H), 1.22 (s, 3H), 1.34 (s, 9H), 1.38 (s, 3H), 1.86-1.91 (m, 1H), 2.08-2.27 (m, 1H),3.02-3.03 (m, 1H), 3.46-3.58 (m, 4H), 3.64-3.74 (m, 2H), 3.89 (s,1H), 4.29-4.49 (m, 3H), 4.47-4.56 (m, 2H), 4.98-5.02 (m, 2H), 5.23 (d, 1H, *J* = 17.1 Hz), 5.86-5.99 (m, 1H), 6.43-6.46 (d, 1H) 6.99-7.35 (m, 3H), 8.45 (d, 1H,*J* = 7.5 Hz);^{13}CNMR (DMSO-d_6,75 MHz) (δ, ppm): 15.72, 24.02, 26.35, 25.13, 27.94, 32.86, 33.03, 39.03, 56.20, 60.36, 70.40, 83.22, 83.81, 84.29, 110.0, 114.92 (d, *J* = 17.0 Hz), 116.95 (d, *J* = 16.8 Hz), 116.59, 119.58, 135.16, 142.70, 153.60, 153.81, 154.78, 123.02-123.13 (dd, *J* = 5.8, 2.5 Hz), 138.91-139.04 (dd, *J* = 6.0, 3.5 Hz), 146.04-149.41 (dd, *J* = 240.8, 12.2 Hz), 147.52-150.93(dd, *J* = 242.7, 12.7 Hz); Mass (m/z): 650.4 (M+1).

***tert*-butyl [(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]{3-[(3a*S*,4*R*,6*S*,6a*R*)-6-(2-hydroxyethoxy)-2,2-dimethyl tetrahydro-3a*H*-cyclopenta[4,5-*d*][1,3]dioxol-4-yl]-5-(prop-2-en-1-ylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*] pyrimidin-7-yl}carbamate (20).**

Compound **19** (100 g, 0.154mol) was dissolved in Toluene (800 ml) and cooled to 10-15 °C. Sodium nitrite (13.0 g, 0.188mol) was dissolved in water (50 ml) and was slowly added to the above reaction mass at 10-15°C. Acetic acid (55 g, diluted with Toluene 50 ml) was slowly added to the above reaction mass at same temperature. Reaction mass temperature was adjusted to 15-20°C and maintained for 60 min. after completion of reaction, water (300 ml) was added to the reaction mass and pH of reaction mass was adjusted to 8.0-8.5 with sodium carbonate solution. Organic layer was separated and extracted with Toluene (200 ml). Organic layer were mixed and washed with 20% sodium chloride solution (200 ml). Organic layer was then concentrated under vacuum at below 55°C to get 101glight brown residue of compound **20**with some traces of Toluene solvent, yield 99.3%.^{1}HNMR(DMSO-d_6,300 MHz) (δ, ppm): 1.28-1.30 (m, 1H), 1.28 (s, 3H), 1.40 (s, 9H), 1.49 (s, 3H), 2.22-2.26 (m, 1H), 2.55-2.76 (m, 2H), 3.22-3.50 (m, 6H), 3.80 (d, 2H,*J* = 6.6 Hz), 4.01-4.06 (m, 1H), 4.55 (bs, 1H), 4.71 (dd, 1H,*J* = 3.0, 6.0 Hz), 5.12-5.29 (m, 3H), 5.32 (d, 1H,*J* = 17.1 Hz), 5.91-6.05 (m, 1H), 7.09-7.37 (m, 3H);Mass (m/z): 661.4 (M+1).

(1*S*,2*S*,3*R*,5*S*)-3-[7-{[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]amino}-5-(prop-2-en-1-ylsulfanyl)-3*H*-[1,2,3] triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (21).

To a compound **20** (100 g), Methanol (150 ml) was added and cooled to 0 °C. HCl solution (230 g, 1.89 mol) was added slowly by maintaining temperature at 0-10 °C, reaction temperature was adjusted to 15 °C and maintained for 3-4 hrs. After completion of reaction water (500 ml), Ethyl acetate (500 ml) was added and pH of the reaction mass was adjusted to 8.5 - 9.5 with sodium carbonate solution. Organic layer was separated and aqueous layer was extracted with Ethyl acetate (200 ml). Both the organic layers were mixed and washed with 20% Sodium chloride solution (200 ml). Organic layer was treated with activated carbon (5 g) and concentrated under vacuum below 55 °C. Hexanes (800 ml) was added slowly at 50-60 °C to the reaction mass, maintained for 60 min and then slowly cooled it to 25-30 °C and maintained for 5-6 hrs. Filtered the slurry and washed it with Ethyl acetate and hexanes mixture (1:1) (100 ml). Ethyl acetate (400 ml) was added to the filtered wet material and heated to 50-60 °C, hexanes (400 ml) was added slowly to it and maintained it for 60 min, slurry was cooled to 25-30 °C and maintained for 5-6 hr, filtered and dried at 45-55 °C to yield 68 g of Off-white compound **21**, yield 86.3%. Melting range 131.2-136.4 °C. ^{1}HNMR (DMSO-d_6,300 MHz) (δ, ppm): 1.34-1.58 (m, 2H), 1.98-2.27 (m, 2H), 2.59-2.69 (m, 1H), 3.13-3.16 (m, 1H), 3.44-3.52 (m, 4H), 3.56-3.68 (m, 1H), 3.75-3.82 (m, 1H), 3.94 (bs, 1H), 4.1-4.15 (m, 1H), 4.52-4.60 (m, 2H), 4.93-5.08 (m, 2H), 5.02-5.36 (m, 3H), 5.74-5.98 (m, 1H), 7.05-7.08 (m, 1H), 7.22-7.37 (m, 2H), 9.42 (d, 1H,*J* = 3.9 Hz);^{13}CNMR (DMSO-d_6,75 MHz) (δ, ppm): 15.04, 24.06, 33.08, 33.34, 34.08, 60.32, 60.52, 70.86, 73.71, 74.48, 81.77, 114.86 (d, *J* = 17.3 Hz), 117.01 (d, *J* = 16.8 Hz), 117.20, 123.22, 134.16, 150.77, 154.04,

168.45, 122.76-122.88 (dd, *J* = 5.9, 3.0 Hz), 139.15-139.27 (dd, *J* = 6.0, 3.5 Hz), 146.11-149.49 (dd, *J* = 241.5, 12.3 Hz), 147.69-150.93(dd, *J* = 242.9, 12.5 Hz); Mass (m/z): 521.4 (M+1).

(1*S*,2*S*,3*R*,5*S*)-3-[7-{[(1*R*, 2*S*)-2-(3,4-difluorophenyl)cyclopropyl]amino}-5-(propylsulfanyl)-3*H*-[1,2,3] triazolo [4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (Ticagrelor, 1).

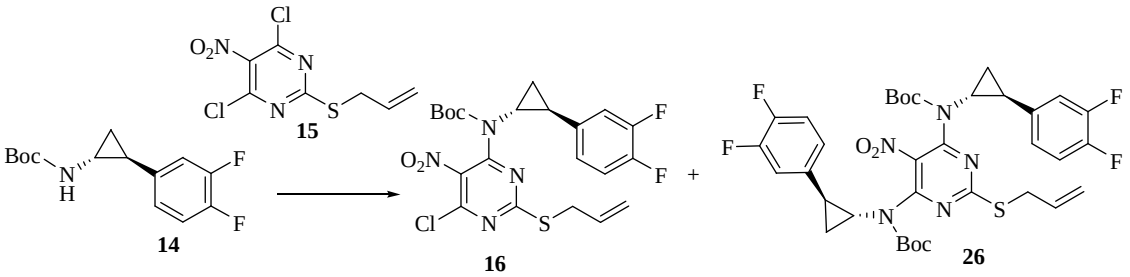
To a compound **21** (100 g, 0.192mol), Tetrahydrofuran (100 ml), Ethanol (600 ml) was added and cooled to -5°C, hydrazine hydrate (85.0 g, 1.36mol) was added to it. Solution of Sodium per iodate (50 g, 0.234mol) dissolved in water (400ml) was added to the above solution at same temperature, slowly raised the temperature up to 50-55°C and maintained for 60 min. After completion of reaction, temperature was cooled to 10-15°C and filtered the reaction mass and washed the inorganics with Tetrahydrofuran (25 ml). Dichloromethane (2000 ml) was added to the filtrate, separated organic layer and washed with 1N sodium hydroxide solution (1200 ml) and then water (300 ml) followed by 25% Sodium chloride solution (300 ml). Organic layer was dried on sodium sulphate (200 g) and then distilled out to get residue. Obtained residue was dissolved in Ethyl acetate (500 ml) and heated up to 55-60°C, hexanes (500 ml) was added at same temperature and maintained it for 60min. Temperature was gradually cooled to room temperature and maintained for 4 hr filtered the material and washed with Ethyl acetate and hexanes mixture (1:1) (100 ml). Obtained material was dried under vacuum at 40-50°C to get 86g of dry Ticagrelor (**1**), yield 85.7% Purity: >99.8%, individual impurity less than 0.05%.

RESULTS AND DISCUSSION

We have been interested in designing a simple and an efficient synthesis and characterization for bioactive target compounds, which remains a challenging area, despite impressive progress in organic synthesis. The aim of present work is synthesis of Ticagrelor (**1**) using novel route. The development of alternate route is useful in the synthesis of pharmaceutical product provides means to find methods which are advantageous in an economic sense, from the technical point of view or otherwise, in particular for large scale manufacture.

The advantage of this route is that the yield at each stage is quantitative which reduces the cost of the product. During optimization of compound**16,** different bases like t-BuOK, LHMDS, n-Butyl lithium were studied along with Sodium Hydride. Double condensed product **26**, was higher with other bases as compared to NaH. The results of studies are summarized in below table.

Base	NaH	t-BuOK	LHMDS	n-Butyl Lithium
Product **16**(%)	94	72	64	68
Impurity **26** (%)	3	15	18	12
Other impurity (%)	1.3	5	6.2	8.4



Scheme-5. Reagents and conditions: Base, THF, Hexanes, -20°C

There are various reports in the literature for the reduction of nitro group like Palladium on Carbon [11,12], Zinc [13,14], Iron powders [15,16]. But the reduction of **18**was carried out using sodium dithionite and Na_2CO_3 in acetone, provided the **19**. The advantage of this reagent is that it is very cheap reagent, there is no any emulsion formation observed in work up as it was observed in Zinc and Iron powder reactions and hence it is very easy in the operations at plant level for scale-up with quantitative yields.

Reduction of carbon-carbon double bond is normally accomplished by using hydrogen and heterogeneous transition metal catalysts e.g. Rh/C, Pd/C, PtO_2 or $NaBH_4$ but in view of scale-up and cost, the reaction is optimized with the hydrazine hydrate and sodium periodate. Reduction of **21** with Pd/C & Pt/C gave multiple impurities like de-fluorinated, de-sulphurization impurities and reactions were very slow as the Sulphur was poisoning the catalyst. Reduction of **21** using Hydrazine hydrate and $NaIO_4$ is very clean reaction which gets completed in 1-2 hrs only and with-out any side impurities. $NaIO_4$oxidizeshydrazine to give Hydrogen, Nitrogen and water, Hydrogen reduces the double bond selectively without disturbing any other functional group & product conversion is 99%.

CONCLUSION

In summary, we have demonstrated the synthesis of Ticagrelor using scheme-3 & scheme-4. The methodology is not only efficient and practical but also useful for industrial scale up as the reagents and chemicals are cheaper and easily available.

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REFERENCES

[1] L Haibo; Hu Ge; Yong Peng; Peigen Xiao; Jun Xu; *Biophysical Chemistry*, **2011**, *155*, 74.
[2] S Brian; B Andrew; B Patrick; N B Timothy; V B Roger; C B Roger; C David; D John; D G Simon; G H Robert; F H Simon; I Francis; H I Anthony; P K Ian; D L Paul; J L Richard; P M Barrie; F M Dermot; P M Michael; W P Stuart; P Garry; P Anil; Aaron *Bioorg. Med. Chem. Let.*, **2007,** 17, 6013.
[3] *Drugs of Future***2007**, 32, 845.
[4] The Clopidogril in unstable angina to Prevent Recurrent Events Trial Investigators (CURE). N. *Engl.J. Med*. **2001**, 345, 494. Durham, P. L.; Dong, P. X.; Belasco, K. T.; Kasperski, J.; Gierasch, W. W.; Edvinsson, L.; Heistad, D. D.; Faraci, F. M.; A. F. Russo, *BrainResearch*, **2004**,99,7103.
[5] Simon Guile; Anthony Ingall; Brian Springthorpe; Paul Willis; US 6251910.
[6] Amoore J. E., Hautala E. *J. Appl Toxicol*. **1983,** 3(6), 272.
[7] "Osmium tetroxide as (Os)". Documentation for Immediately Dangerous to Life or Health Concentrations (IDLHs), Centers for Disease Control.
[8] Ting-Yueh Tsai, Tsu Hsu, Chinung-Tong Chen, Jai-Hong Cheng, Teng-Kuang Yeh, Xin Chen, Chung-Yu Huang, Chung-Nien Chang, Su-Huei Hsieh, *Bioorg. Med. Chem.*, **2009**, 17, 2388.
[9] Hao Zhang, Jun Liu, Luyong Zhang, Lingyi Kong, HequanYao, Hongbin Sun. *Bioorg. Med. Chem.*, **2012**, 22,3598.
[10] Brock T. Shireman & Marvin J. Miller; *Tetrahedron Lett.* **2000**, 41, 9537.
[11] G. S. Vanier, *Synlett*, **2007**, 131.
[12] H. Berthold, T. Schotten, H. Hönig, *Synthesis*, **2002**, 1607.
[13] T. Schabel, C. Belger, B. Plietker, *Org. Lett.*, **2013**, 15, 2858.
[14] A. Porzelle, M. D. Woodrow, N. C. O. Tomkinson, *Synlett*, **2009**, 798.
[15] S. Chandrappa, T. Vinaya, T. Ramakrishnappa, K. S. Rangappa, *Synlett*, **2010**, 3019.
[16] A. L. Korich; T. S. Huges; *Synlett*, **2007**, 2602.