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Total synthesis of a thromboxane receptor antagonist, terutroban†

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A total synthesis of terutroban is achieved using the Claisen rearrangement, Friedel–Crafts acylation and Heck coupling as key reactions, avoiding the classical Diels–Alder approach used before.

Introduction

Thromboxane A_2 (**1a**, Fig. 1), an unstable metabolite of arachidonic acid, is responsible for a wide range of pulmonary, renal, circulatory and other disorders. Thromboxane A_2 causes irreversible platelet aggregation, vasoconstriction and smooth muscle cell proliferation. It is released from activated platelets, monocytes and damaged vessel walls. The activity of thromboxane A_2 is through the thromboxane-type prostanoid (TP) receptor extensively present on platelets and vascular smooth muscle. TP receptor agonists and thromboxane A_2 synthase inhibitors are potential antiplatelet agents. Many of these are also TP receptor agonists and have very short half-lives.[1] Thus, there is always a requirement for a more effective, selective and long-lasting thromboxane receptor antagonist. In one of the studies to find a selective antagonist, it was observed that compounds containing a carboxylic acid and a benzenesulfonamide group separated by a spacer were found to be the best among the compounds tested. Ramatroban (**1b**),[2] (Fig. 1) a compound with these features, marketed as Baynas® by Bayer and Nippon Shinyaku Co. for allergic rhinitis, is a selective TP receptor antagonist. The pharmacophore was further explored by Lavielle *et al.*, which led to the identification of a tetrahydronaphthalene derivative, terutroban (**2**) (Fig. 1) as a TP receptor antagonist. The only reported synthesis of **2** to date is achieved using Diels–Alder as the key reaction between an appropriate 2-pyrone and an acetylenic derivative.[3] Terutroban is being developed by the Institut de Recherches Servier (France) and has entered Phase III clinical trials under PERFORM (*p*revention of cerebrovascular *e*vents of ischemic origin with te*r*utroban in patients with a history o*f* ischemic stro*k*e or t*r*ansient ische*m*ic attack). The study was prematurely stopped, and the reasons and results have not been disclosed. Nonetheless, the skeleton attracted our attention due to our interest in molecules with important biological activities, including the synthesis of prostanoids, beraprost (antiplatelet drug)[4] and iloprost (drug for pulmonary arterial hypertension).[5] We wish to explore a non-Diels–Alder approach for the synthesis of this molecule which can be further extended to synthesize analogues.

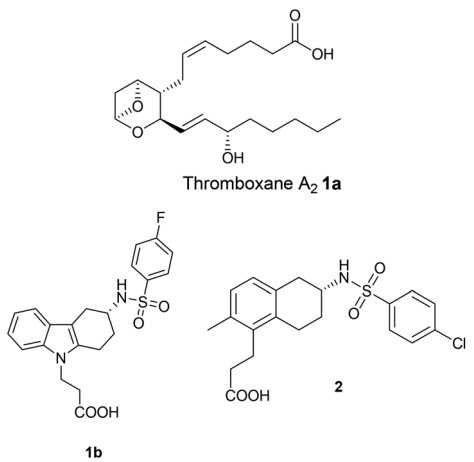

Fig. 1 Structure of ramatroban (**1**) and terutroban (**2**).

Present work

In general, the tetralin units, such as that present in terutroban, are built using a Diels–Alder reaction.[6] The reported synthesis of terutroban considered the molecule as a substituted benzene analogue which was built by a Diels–Alder reaction, as is the norm. We explored the synthesis of **2** as a tetrahydronaphthalene analogue built starting from a benzene ring. In a retrosynthetic analysis, (Fig. 2) terutroban can be synthesized

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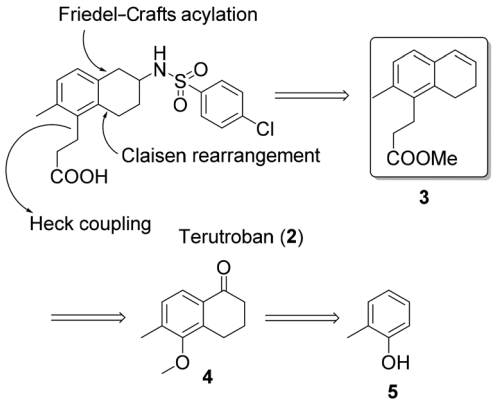
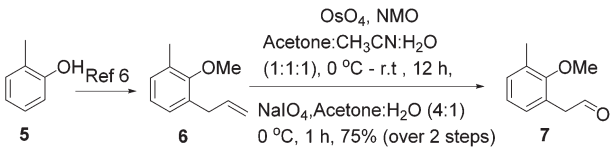


Fig. 2 Retrosynthetic analysis.

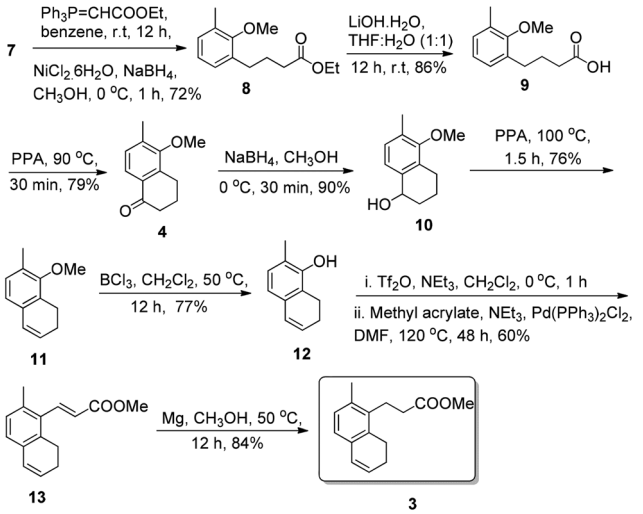
from olefin **3** in six steps involving sulphonamidation under Mitsunobu conditions. Compound **3** can be obtained from **4** in five sequential steps using dehydration and Heck coupling as the key reactions. The tetralone **4** in turn can be synthesized starting from commercially available *o*-cresol **5** in seven steps involving o-allylation, Claisen rearrangement, oxidative olefin cleavage, Wittig olefination, olefin reduction, ester hydrolysis and a Friedel–Crafts acylation reaction.

The use of an easily available and low cost starting material, *o*-cresol (~15 USD Kg^{-1}), was considered to enable a facile, large scale synthesis of the target molecule **2**. Thus *o*-cresol gave **6** following a known sequence.[7] Lemieux–Johnson oxidation–dihydroxylation with catalytic osmium tetraoxide followed by carbon–carbon bond cleavage using sodium periodate resulted in aldehyde **7** in 75% yield over two steps (Scheme 1).

Wittig olefination with carbethoxymethylene triphenylphosphorane delivered the olefin, which upon reduction with sodium borohydride and $NiCl_2{\cdot}6H_2O$ gave **8** in 72% yield over two steps. Hydrolysis of the ester using lithium hydroxide afforded **9** (86% yield), and intramolecular Friedel–Crafts acylation with PPA resulted in tetralone **4** in 79% yield. Reduction of the ketone with sodium borohydride at 0 °C provided alcohol **10** in 90% yield, followed by dehydration of the secondary alcohol with PPA[8] at 100 °C which gave **11** in 76% yield. Demethylation of the phenolic methyl ether using boron trichloride[9] afforded **12** in 77% yield. Conversion of the phenolic hydroxyl group to a triflate followed by Heck coupling[10] with methyl acrylate in presence of bis(triphenylphosphine)-palladium(II) chloride provided unsaturated ester **13** in 60% yield over two steps. The double bond in **13** was selectively reduced with magnesium in methanol[11] to yield the key intermediate **3** in 84% yield. Compound **3** has both the rings and



Scheme 1 Synthesis of intermediate **7**.



Scheme 2 Synthesis of key intermediate **3**.

the required functional groups to synthesize the target molecule (Scheme 2).

The next logical step was to synthesize an aziridine[12] analogue, which can be selectively opened to obtain the target molecule. The reaction of sodium chloro(4-chlorophenyl)sulfonyl amide and iodine at pH 7 buffer with **3** did not yield the required product. Other different reaction conditions also did not yield the required aziridine.

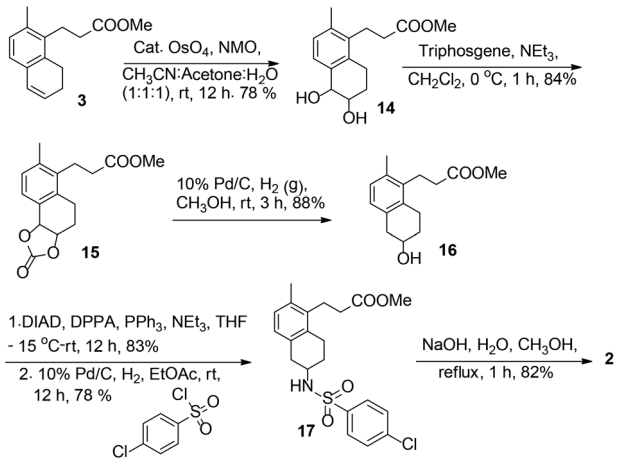
As the desired aziridine was not obtained, the next effort was to synthesize an epoxide and open it to obtain an alcohol. Thus, an epoxidation reaction was tried with *m*CPBA, H_2O_2-titanium isopropoxide, H_2O_2 *etc*.[12] The reaction always resulted in an inseparable mixture of compounds.

A stepwise approach was then followed to synthesize **2**. Thus, key intermediate **3** was reacted with osmium tetroxide to get diol **14** in 78% yield. Diol **14** was converted to a carbonate derivative with triphosgene[13] with 84% yield, which on reduction with 10% Pd/C under hydrogenation conditions[14] afforded alcohol **16** in 88% yield. Mitsunobu conditions[15] were employed to convert the alcohol to an azide in 83% yield. Reduction over 10% Pd/C under hydrogenation conditions[16], followed by *in situ* conversion of the amine, provided the ester **17** in 78% yield. Hydrolysis of the ester with sodium hydroxide[3] gave terutroban **2**, in 82% yield, which resembled the reported acid in all respects (Scheme 3).

Experimental

General

^1H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200, Bruker Avance 300 or Varian Innova 500 at 75, 125, 300 or 500 MHz in $CDCl_3$ or DMSO(D_6) solvent at ambient temperature. Chemical shifts δ are given in ppm, coupling constants J are in Hz. The chemical shifts are reported in ppm on a scale downfield from TMS as the internal standard, and signal patterns are indicated as follows: s, singlet; d, doublet;



Scheme 3 Synthesis of terutroban **2**.

dd, doublet of doublets; dt, doublet of triplets; t, triplet; m, multiplet; bs, broad singlet, quin., quintet. FT-IR Spectra: a Perkin Elmer FT-IR was used to record spectra as KBr thin films or neat; ν_{max} are given in cm^{-1}. ESI- and HR-ESI-MS were recorded using a Finnigan MAT 1020B; values are given in *m*/*z*. All the reagents and solvents were reagent grade and used without further purification unless specified otherwise. Technical grade ethyl acetate and hexanes used for column chromatography were distilled prior to use. Column chromatography was carried out using silica gel (60–120 mesh) packed in glass columns. All the reactions were performed under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring.

2-(2-Methoxy-3-methylphenyl)acetaldehyde (7). To a solution of **6** (28.5 g, 175 mmol) in acetone–acetonitrile–water (1 : 1 : 1) (300 mL), were added OsO_4 (44 mg, 0.18 mmol) and NMO (41.16 g, 351 mmol). The reaction was stirred at room temperature for 12 h, quenched with aqueous sodium sulphite solution and stirred for an additional 30 min. The solution was concentrated *in vacuo* to remove organic solvents. The aqueous phase was extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (1 : 1 hexanes–EtOAc) to afford diol (29.3 g, 85%) as a colorless thick liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11–6.95 (m, 3H), 4.17–4.03 (m, 1H), 3.95–3.86 (m, 2H), 3.76 (s, 3H), 3.60 (dd, J = 11.5, 3.2 Hz, 1H), 3.46 (q, J = 5.7 Hz, 1H), 2.92–2.78 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 131.0, 130.6, 130.0, 128.9, 124.3, 72.8, 65.8, 60.3, 31.2, 16.1; IR (KBr): ν_{max} 3382, 2942, 1246, 753 cm^{-1}; HRMS (ESI): Calcd for $C_{11}H_{16}O_3Na$ $[M + Na]^+$: 219.0991, found: 219.0989.

To a solution of diol (29.2 g, 148 mmol) in acetone–water (4 : 1, 400 mL) was added sodium periodate (63.6 g, 297 mmol). The reaction mixture was stirred at 0 °C for 1 h. Upon completion of the reaction, it was filtered on celite and the filtrate was concentrated *in vacuo* to remove acetone. The aqueous phase was extracted with ethyl acetate (3 × 150 mL), washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography (9 : 1 hexanes–EtOAc) to afford **7** (21.6 g, 88%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9. 9.72 (t, J = 2.3 Hz, 1H), 7.19–7.12 (m, 1H), 7.02 (d, J = 5.3 Hz, 2H), 3.69 (s, 3H), 3.68 (dd, J = 2.3, 0.8 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 157.1, 131.3, 131.0, 128.9, 125.6, 124.3, 60.0, 45.3, 16.1; IR (KBr): ν_{max} 2937, 1731, 1248, 1124, 752 cm^{-1}; HRMS (ESI): Calcd for $C_{10}H_{13}O_2$ $[M + H]^+$: 165.0910, found: 165.0911.

Ethyl 4-(2-methoxy-3-methylphenyl)butanoate (8). To a solution of **7** (21.4 g, 130 mmol) in benzene (200 mL) was added carbethoxymethylene triphenylphosphine (54.42 g, 156 mmol). The reaction mixture was stirred at rt for 12 h under a nitrogen atmosphere, after which it was concentrated *in vacuo*. The crude was purified by column chromatography (19 : 1 hexanes–EtOAc) to afford the olefinic compound (25.3 g, 83%) as a light yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.11 (m, 1H), 7.10–7.05 (m, 1H), 6.99–6.96 (m, 2H), 5.79 (dt, J = 15.7, 1.5 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.71 (s, 3H), 3.55 (dd, J = 6.6, 1.5 Hz, 2H), 2.30 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 156.7, 147.5, 131.2, 130.0, 128.1, 124.1, 122.1, 119.6, 60.5, 60.1, 32.5, 16.1, 14.2; IR (KBr): ν_{max} 2930, 1719, 1654, 1183, 1036, 770 cm^{-1}; HRMS (ESI): Calcd for $C_{14}H_{18}O_3Na$ $[M + Na]^+$: 257.1148, found: 257.1145.

To a solution of olefin (25 g, 106 mmol) in methanol (300 mL) was added $NiCl_2{\cdot}6H_2O$ (25.3 g, 106 mmol). The mixture was cooled to 0 °C and $NaBH_4$ (8 g, 213 mmol) was added portion-wise. Upon completion of the reaction, as indicated by TLC, it was filtered on celite and concentrated *in vacuo*. The crude mixture was quenched with aq. saturated NH_4Cl (40 mL). The aqueous phase was extracted with ethyl acetate (2 × 150 mL), washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (19 : 1 hexanes–EtOAc) to afford **8** (21.9 g, 87%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05–7.0 (m, 2H), 6.99–6.92 (m, 1H), 4.13 (q, J = 6.8 Hz, 2H), 3.72 (s, 3H), 2.67 (t, J = 7.5 Hz, 2H), 2.35 (t, J = 6.8, 2H), 2.29 (s, 3H), 1.95 (quin., J = 7.5 Hz, 2H), 1.26 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 156.7, 134.2, 130.9, 129.2, 127.7, 123.9, 60.3, 60.1, 33.9, 29.1, 25.9, 16.1, 14.2; IR (KBr): ν_{max} 2945, 1734, 1245, 1017, 753 cm^{-1}; HRMS (ESI): Calcd for $C_{14}H_{20}O_3Na$ $[M + Na]^+$: 259.1304, found 259.1295.

4-(2-Methoxy-3-methylphenyl)butanoic acid (9). To a solution of **8** (20.8 g, 87.89 mmol) in THF–H_2O (1 : 1) (200 mL) was added $LiOH{\cdot}H_2O$ (18.4 g, 439 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated *in vacuo* to remove THF. Organic impurities were extracted with ethyl acetate (1 × 100 mL). The aqueous phase was cooled to 0 °C and the pH was adjusted to 2 by the addition of 2N aq. HCl. The aqueous phase was extracted with ethyl acetate (3 × 100 mL), washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford **9** (15.8 g, 86%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06–7.0 (m, 2H), 6.99–6.92 (m, 1H), 3.72 (s, 3H), 2.69 (t, J = 7.5 Hz, 2H), 2.41 (t, J = 7.4 2H), 2.29 (s, 3H), 1.96 (quin.,

J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.9, 156.8, 134.0, 131.0, 129.3, 127.8, 123.9, 60.3, 33.6, 29.1, 25.5, 16.2; IR (KBr): ν_{max} 2942, 2673, 1710, 1244, 1013, 753 cm^{-1}; MS (ESI): m/z 207 $[M - H]^+$.

5-Methoxy-6-methyl-3,4-dihydronaphthalen-1-(2*H*)-one (4). Compound **9** (15.7 g, 75.41 mmol) was subjected to an intramolecular Friedel–Crafts acylation with PPA (50.96 g, 150 mmol) at 90 °C for 3 min, followed by an second addition of hot PPA (38 g, 113 mmol), and the resultant mixture was stirred for 30 min. Ice (100 mL) was then placed into the reaction flask. The flask was allowed to cool and the mixture was extracted with ethyl acetate (3 × 100 mL). The organic layer was washed with 5% NaOH (2 × 100 mL), H_2O (2 × 100 mL), 3% CH_3COOH (1 × 100 mL), 5% $NaHCO_3$ (1 × 100 mL) and brine (1 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude was purified by column chromatography (9 : 1 hexanes–EtOAc) to afford **4** (11.3 g, 79%) as an orange liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 7.9 Hz, 1H), 7.14 (d, J = 7.9 Hz, 1H), 3.75 (s, 3H), 2.97 (t, J = 6.0, 2H), 2.62 (t, J = 6.2 Hz, 2H), 2.34 (s, 3H), 2.11 (quin., J = 6.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 155.7, 137.5, 137.1, 132.2, 129.0, 122.8, 59.8, 38.7, 23.4, 22.8, 16.5; IR (KBr): ν_{max} 2943, 1683, 1283, 1018, 767 cm^{-1}; HRMS (ESI): Calcd for $C_{12}H_{15}O_2$ $[M + H]^+$: 191.1066, found 191.1065.

5-Methoxy-6-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (10). To a solution of **4** (11.12 g, 58.46 mmol) in CH_3OH (100 mL) was added $NaBH_4$ (2.65 g, 70.16 mmol) portion-wise at 0 °C. The reaction was allowed to stir for 30 min at the same temperature. After completion of the reaction, as indicated by TLC, the reaction was quenched with aq. saturated NH_4Cl solution (20 mL). The reaction mixture was concentrated under reduced pressure and aq. saturated NH_4Cl (50 mL) was added. The aqueous phase was extracted with ethyl acetate (3 × 60 mL), washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (6 : 1 hexanes–EtOAc) to afford **10** (10.2 g, 90%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 8.3 Hz, 1H), 7.04 (d, J = 7.5 Hz, 1H), 4.77–4.72 (m, 1H), 3.71 (s, 3H), 2.86 (dt, J = 18.9, 5.3 Hz, 1H), 2.64 (dt, J = 17.4, 6.0 Hz, 1H), 2.27 (s, 3H), 1.98–1.85 (m, 2H), 1.84–1.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 138.1, 130.4, 129.8, 128.7, 124.2, 67.9, 59.4, 31.9, 23.4, 18.3, 15.9; IR (KBr): ν_{max} 3382, 2937, 1453, 1015, 820 cm^{-1}; MS (ESI): m/z 215 $[M + Na]^+$.

8-Methoxy-7-methyl-1,2-dihydronaphthalene (11). Compound **10** (10.0 g, 52.18 mmol) and PPA (88 g, 260 mmol) were stirred at 100 °C for 1.5 h. After cooling to room temperature, the mixture was diluted with water and basified with ammonium hydroxide (200 mL). The aqueous phase was extracted with chloroform (3 × 100 mL), washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (99 : 1 hexanes–EtOAc) to afford **11** (6.9 g, 76%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (d, J = 7.5 Hz, 1H), 6.73 (d, J = 7.5 1H), 6.43 (dt, J = 9.8, 1.5 Hz, 1H), 6.02–5.94 (m, 1H), 3.70 (s, 3H), 2.83 (t, J = 8.3 Hz, 2H), 2.33–2.24 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 133.5, 129.9, 128.4, 127.7, 127.6, 121.8, 59.9, 22.8, 20.5, 16.1; IR (KBr): ν 2934, 1566, 1086, 826 cm^{-1}; MS (ESI): m/z 197 $[M + Na]^+$.

2-Methyl-7,8-dihydronaphthalen-1-ol (12). A solution of **11** (6.8 g, 39.21 mmol) in dry CH_2Cl_2 (30 mL) was cooled to 0 °C and BCl_3 (1 M, 78.4 mL, 78.41 mmol) was added to it dropwise. The reaction mixture was warmed to rt and heated to reflux temperature. The reaction was quenched with water (50 mL) and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (19 : 1 hexanes–EtOAc) to afford **12** as a red oil (4.8 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (d, J = 7.4 Hz, 1H), 6.58 (d, J = 7.5 Hz, 1H), 6.41 (dt, J = 9.6, 1.9 Hz, 1H), 6.0–5.91 (m, 1H), 4.64 (s, 1H), 2.74 (t, J = 8.3 Hz, 2H), 2.37–2.28 (m, 2H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 133.2, 127.9, 127.7, 127.1, 122.6, 119.9, 118.7, 22.6, 19.9, 15.9; IR (KBr): ν_{max} 3469, 2928, 1658, 823 cm^{-1}; HRMS (ESI): Calcd for $C_{11}H_{13}O$ $[M + H]^+$: 161.0960, found: 161.0963.

(*E*)-Methyl 3-(2-methyl-7,8-dihydronaphthalen-1-yl)acrylate (13). To a solution of **12** (4.7 g, 29.4 mmol) in dry CH_2Cl_2 (50 mL) was added NEt_3 (12 mL, 88.2 mmol), followed by a slow addition of triflic anhydride (5.9 mL, 35.28 mmol) at 0 °C. The mixture was stirred at same temperature for 1 h. The reaction was quenched with a slow addition of aq. 1 N HCl (30 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (hexanes) to afford triflate (6.9 g, 81%) as a light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (dd, J = 7.6, 0.6 Hz, 1H), 6.94 (d, J = 7.6, 1H), 6.45 (dt, J = 9.6, 1.8 Hz, 1H), 6.09–6.05 (m, 1H), 2.87 (t, J = 8.3 Hz, 2H), 2.36 (s, 3H), 2.33–2.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 134.6, 129.8, 129.6, 129.1, 128.5, 126.8, 125.6, 22.2, 21.7, 17.0; IR (KBr): ν 2930, 1556, 1410, 1215, 771 cm^{-1}; MS (ESI): m/z 293 $[M + H]^+$.

$PdCl_2(PPh_3)_2$ (31.9 mg, 2 mol%) was added to a degassed solution of triflate (6.8 g, 23.27 mmol), methyl acrylate (10.5 mL, 116 mmol) and NEt_3 (9.8 mL, 69.81 mmol) in DMF (50 mL). The reaction mixture was stirred at 120 °C under an argon atmosphere for 48 h. Ice water (50 mL) was then added to it. The aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (29 : 1 hexanes–EtOAc) to afford **13** as a red oil (3.9 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 16.5 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.44 (dt, J = 9.5, 1.7 Hz, 1H), 6.03–5.99 (m, 2H), 3.82 (s, 3H), 2.81 (t, J = 8.2 Hz, 2H), 2.31 (s, 3H), 2.29–2.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 143.4, 135.3, 133.5, 133.0, 132.3, 127.9, 127.8, 127.7, 126.3, 124.3, 51.7, 24.9, 23.1, 20.8; IR (KBr): ν_{max} 2949, 1722, 1641, 1169, 772 cm^{-1}; HRMS (ESI): Calcd for $C_{15}H_{17}O_2$ 229.1223 $[M + H]^+$, found: 229.1224.

Methyl 3-(2-methyl-7,8-dihydronaphthalen-1-yl)propanoate (3). To a solution of **13** (3.75 g, 16.43 mmol) in CH_3OH (40 mL) were added Mg turnings (788 mg, 32.87 mmol). The reaction mixture was heated at reflux temperature for 12 h. After completion of the reaction, as indicated by TLC, the solvent was removed under reduced pressure. The reaction mixture was partitioned between aq. saturated NH_4Cl and ethyl acetate. The aqueous phase was extracted with ethyl acetate (2 × 40 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (29 : 1 hexanes–EtOAc) to afford **3** (3.17 g, 84%) as a liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, J = 7.5 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.42 (dt, J = 9.5, 1.8 Hz, 1H), 6.0–5.96 (m, 1H), 3.71 (s, 3H), 3.01–2.96 (m, 2H), 2.79 (t, J = 8.2 Hz, 2H), 2.47–2.42 (m, 2H), 2.33–2.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 135.7, 135.2, 133.4, 132.4, 128.2, 128.1, 127.2, 124.5, 51.7, 33.6, 24.4, 23.7, 23.3, 19.9; IR (KBr): ν_{max} 2926, 1738, 1219, 772 cm^{-1}; HRMS (ESI): Calcd for $C_{15}H_{18}O_2Na$ $[M + Na]^+$: 253.1199, found: 253.1204.

Methyl 3-(5,6-dihydroxy-2-methyl-5,6,7,8-tetrahydro naphthalen-1-yl)propanoate (14). To a solution of **3** (3.1 g, 13.46 mmol) in acetone–acetonitrile–water (1 : 1 : 1, 30 mL) were added OsO_4 (33.7 mg, 0.1 mmol) and NMO (3.15 g, 26.92 mmol). The reaction was stirred at room temperature for 12 h. The mixture was quenched with aq. sodium sulphite solution and stirred for an additional 30 min. The solution was concentrated *in vacuo* to remove organic solvents and 30 mL water was added. The aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (1 : 1 hexanes–EtOAc) to afford **14** (2.5 g, 78%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 7.5 Hz, 1H), 7.08 (d, J = 8.3 Hz, 1H), 4.67 (d, J = 3.8 Hz, 1H), 4.05–3.95 (m, 1H), 3.72 (s, 3H), 3.04–2.91 (m, 3H), 2.78–2.63 (m, 1H), 2.48–2.39 (m, 2H), 2.32 (s, 3H), 2.14–1.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 136.5, 136.3, 134.6, 134.1, 128.8, 128.2, 70.3, 69.0, 51.7, 32.9, 26.0, 24.6, 24.3, 19.6; IR (KBr): ν_{max} 3394, 2933, 1735, 1291, 1198, 773 cm^{-1}; HRMS (ESI): Calcd for $C_{15}H_{20}O_4Na$: 287.1253 $[M + Na]^+$, found 287.1252.

Methyl 3-(7-methyl-2-oxo-3a,4,5,9b-tetrahydronaphtho[2,1-*d*] [1,3]dioxol-6-yl)propanoate (15). To a solution of **14** (2.35 g, 8.89 mmol) in dry CH_2Cl_2 (20 mL) was added NEt_3 (3.7 mL, 26.67 mmol). The solution was cooled to 0 °C and triphosgene (2.64 g, 8.89 mmol) was added slowly in portions. The reaction was stirred at rt for 1 h and quenched with water (20 mL). The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (6 : 1 hexanes–EtOAc) to afford **15** (2.17 g, 84%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, J = 7.9 Hz, 1H), 7.12 (d, J = 7.7 Hz, 1H), 5.68 (d, J = 7.9 Hz, 1H), 5.20–5.12 (m, 1H), 3.71 (s, 3H), 3.06–2.97 (m, 2H), 2.85–2.78 (m, 2H), 2.47–2.27 (m, 6H), 1.98–1.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 154.7, 138.3, 136.7, 136.5, 129.2, 129.1, 127.5, 76.3, 74.9, 51.8, 33.3, 27.2, 24.4, 20.0, 19.9; IR (KBr): ν_{max} 2924, 1796, 1733, 1168, 772 cm^{-1}; HRMS (ESI): Calcd for $C_{16}H_{18}O_5Na$ 313.1046 $[M + Na]^+$, found 313.1043.

Methyl 3-(6-hydroxy-2-methyl-5,6,7,8-tetrahydronaphthalen-1-yl)propanoate (16). To a solution of **15** (2.1 g, 7.23 mmol) in CH_3OH (20 mL) was added Pd/C (45.65 mg, 10% w/w) in sulfur-free conditions. The reaction mixture was stirred under a hydrogen atmosphere at rt for 3 h. After completion, the reaction mixture was filtered through celite and the solvent was evaporated under vacuum. The crude was purified by column chromatography (6 : 1 hexanes–EtOAc) to afford **16** (1.59 g, 88%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, J = 7.7 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H), 4.18–4.08 (m, 1H), 3.72 (s, 3H), 3.11–2.90 (m, 4H), 2.84–2.70 (m, 2H), 2.48–2.39 (m, 2H), 2.30 (s, 3H), 2.15–2.03 (m, 1H), 1.90–1.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 136.6, 133.9, 133.6, 132.3, 128.2, 127.8, 66.7, 51.7, 38.8, 33.0, 31.6, 24.5, 24.3, 19.4; IR (KBr): ν_{max} 3406, 2926, 1736, 1219, 772 cm^{-1}; HRMS (ESI): Calcd for $C_{15}H_{20}O_3Na$ 271.1304 $[M + Na]^+$, found 271.1302.

Methyl 3-(6-(4-chlorophenylsulfonamido)-2-methyl-5,6,7,8-tetrahydronaphthalen-1-yl)propanoate 3-(6-(4-chlorophenyl sulfonamido)-2-methyl-5,6,7,8-tetrahydronaphthalen-1-yl) propanoate (17). Alcohol **16** (1.42 g, 5.72 mmol) and triphenylphosphine (2.24 g, 8.58 mmol) were dissolved in dry THF (20 mL). The mixture was cooled to −15 °C, and diisopropyl azodicarboxylate (DIAD, 2.84 mL, 14.29 mmol) was added to it. After stirring the solution for 10 min at −15 °C, the temperature was raised to 0 °C and diphenylphosphoryl azide (DPPA, 1.79 mL, 8.58 mmol) was added. The solution was stirred for 30 min at 0 °C and then for 12 h at room temperature. Concentration and gradient flash chromatography (99 : 1 hexanes–EtOAc) gave the azide (1.3 g, 83%) as a sticky yellow liquid, which was directly used for the next step.

To a solution of azide (1.3 g, 4.76 mmol) in EtOAc (15 mL) was added Pd/C (6.7 mg, 10% w/w) in sulfur-free conditions followed by 4-chlorobenzene-1-sulfonyl chloride (1.99 g, 9.51 mmol). The reaction mixture was stirred under a hydrogen atmosphere at rt for 12 h. After completion, the reaction mixture was filtered through celite and the solvent was evaporated under vacuum. The crude was purified by column chromatography (4 : 1 hexanes–EtOAc) to afford **17** (1.56 g, 78%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 7.7 Hz, 1H), 6.75 (d, J = 7.7, 1H), 4.76 (d, J = 7.7 Hz, 1H), 3.71 (s, 3H), 3.68–3.57 (m, 1H), 2.97–2.53 (m, 6H), 2.43–2.35 (m, 2H), 2.29 (s, 3H), 2.03–1.91 (m, 1H), 1.83–1.69 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 139.6, 139.1, 136.9, 134.5, 132.9, 131.1, 129.4, 128.5, 128.4, 127.7, 51.8, 49.1, 36.8, 32.9, 29.6, 24.4, 24.0, 19.4; IR (KBr): ν_{max} 2923, 1735, 1162, 772 cm^{-1}; HRMS (ESI): Calcd for $C_{21}H_{25}ClNO_4S$ 422.1187 $[M + H]^+$, found 422.1188.

3-(6-(4-Chlorophenylsulfonamido)-2-methyl-5,6,7,8-tetrahydronaphthalen-1-yl)propanoic acid (2). Compound **17** (1.43 g, 3.39 mmol) was brought to reflux in methanol (15 mL), in the presence of 2 N sodium hydroxide (404 mg, 10.17 mmol) for

1 h. After cooling, the solvent was evaporated *in vacuo*, the mixture was washed with ethyl acetate (1 mL) and the aqueous phase was acidified with 1N HCl. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give terutroban (**2**) (1.12 g, 82%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (d, J = 6.6 Hz, 1H), 7.84 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 7.7 Hz, 1H), 6.69 (d, J = 7.7 Hz, 1H), 3.31(m, 1H), 2.83–2.65 (m, 4H), 2.63–2.54 (m, 2H), 2.30–2.21 (m, 2H), 2.19 (s, 3H), 1.86–1.74 (m, 1H), 1.63–1.50 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.2, 140.7, 137.3, 136.9, 133.5, 133.3, 131.9, 129.5, 128.5, 127.9, 127.1, 49.0, 36.4, 32.9, 29.5, 24.3, 24.2, 19.2; IR (KBr): ν_{max} 2924, 1709, 1219, 772 cm^{-1}; HRMS (ESI): Calcd for $C_{20}H_{23}O_4NClS$ 408.1030 $[M + H]^+$, found 408.1040. [Reported ^{1}H NMR[3a] (DMSO-d_6) δ 12.5 (s, 1H), 7.9 (s, 1H), 7.8 (d, 2H), 7.7 (d, 2H), 6.9–6.7 (d, 2H), 3.3 (m, 1H), 3.0–2.5 (m, 6H), 2.3 (m, 2H), 2.2 (s, 3H), 2.0–1.5 (m, 2H).]

Conclusions

In conclusion, the total synthesis of terutroban is accomplished using a non-Diels–Alder approach. The Claisen rearrangement, Friedel–Crafts acylation and Heck coupling reaction are the key reactions utilized. The utility of cost-effective chemicals together with the flexible route allows one to visualise the design of analogues with ease.

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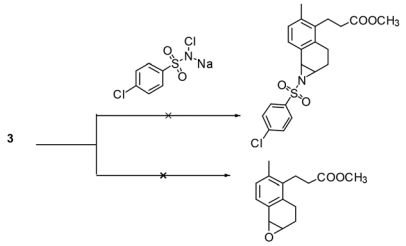

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