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MONOGRAPH

VORAPAXAR

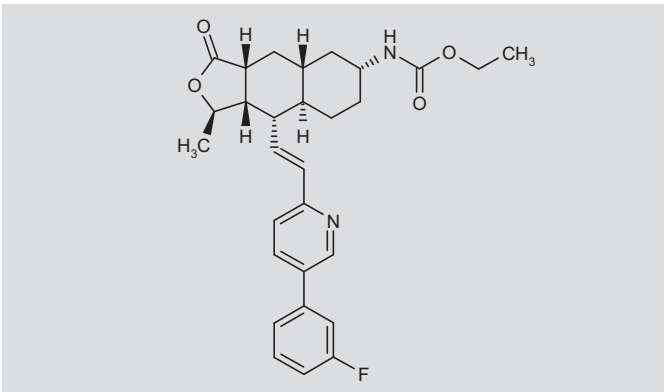
Prop INN; USAN

PAR1 Receptor Antagonist
Antiplatelet Therapy

Sch-530348

N-[(1*R*,3a*R*,4a*R*,6*R*,8a*R*,9*S*,9a*S*)-9-[2-[5-(3-Fluorophenyl)pyridin-2-yl]vinyl]-1-methyl-3-oxoperhydronaphtho[2,3-*c*]furan-6-yl]carbamic acid ethyl ester

InChI: 1S/C29H33FN2O4/c1-3-35-29(34)32-23-10-11-24-20(14-23)15-26-27(17(2)36-28(26)33)25(24)12-9-22-8-7-19(16-31-22)18-5-4-6-21(30)13-18/h4-9,12-13,16-17,20,23-27H,3,10-11,14-15H2,1-2H3,(H,32,34)/b12-9+/t17-,20+,23-,24-,25+,26-,27+/m1/s1



$C_{29}H_{33}FN_2O_4$
Mol wt: 492.5817
CAS: 618385-01-6
CAS: 750634-26-5
EN: 353335

SUMMARY

Atherothrombosis, including myocardial infarction and ischemic stroke, is a highly prevalent disease throughout the world. Platelet activation plays a crucial role in the onset of atherothrombotic events, while detailed mechanisms of platelet pathophysiology contributing to the onset of symptomatic atherothrombotic events have yet to be elucidated. Antiplatelet agents such as aspirin and clopidogrel are the most commonly used. Currently emerging agents exhibit certain limitations and are not capable of satisfactorily preventing the recurrence of atherothrombotic events without increasing the risk of serious bleeding. There are various receptors and activation signaling pathways in platelets, but aspirin and clopidogrel are specific inhibitors of cyclooxygenase COX-1 and the $P2Y_{12}$ receptor, respectively. Vorapaxar (Sch-530348) was developed as a specific inhibitor of the protease-activated receptor PAR1, which is entirely distinct from the previous antiplatelet agents. Results of phase II clinical trials with vorapaxar appear favorable for clinical practice, with a reasonably low rate of bleeding complications. Results of clinical outcome trials with a large enough sample size, along with detailed basic and translational research to further clarify the mechanism of action of vorapaxar, are eagerly awaited.

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SYNTHESIS*

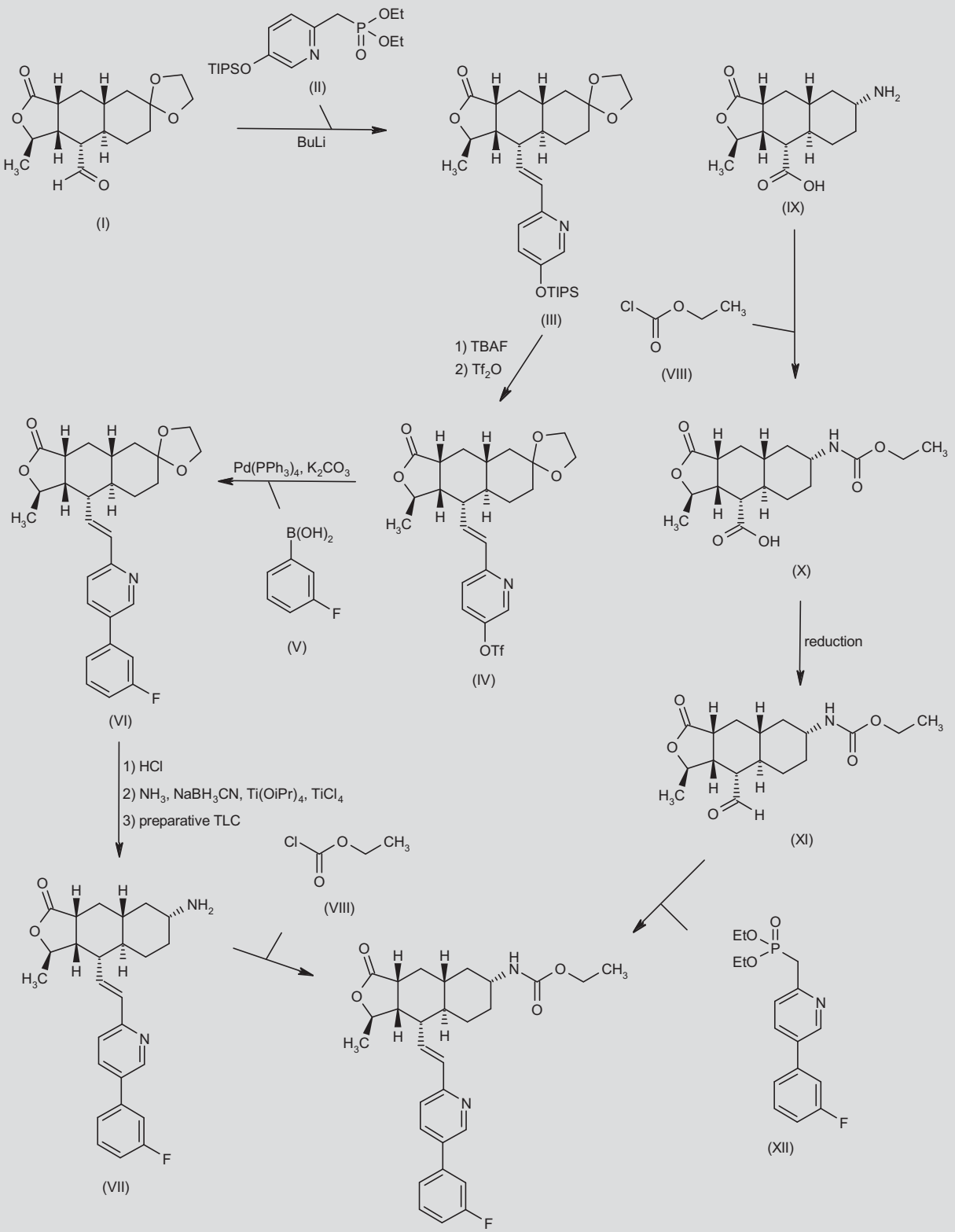
Vorapaxar can be prepared following two alternative strategies:

In one strategy, Horner–Emmons condensation of tetracyclic aldehyde (I) with pyridylmethyl phosphonate (II) by means of BuLi in THF gives the olefin adduct (III), which, after desilylation to the corresponding hydroxypyridine with TBAF in THF, is treated with Tf_2O in pyridine to afford the pyridyl triflate (IV). Suzuki coupling of triflate (IV) with 3-fluorophenylboronic acid (V) by means of $Pd(PPh_3)_4$ and K_2CO_3 in toluene/EtOH/H_2O at 100 °C gives the phenylpyridine derivative (VI). After hydrolysis of the ethylene ketal group in compound (VI) by means of HCl in acetone at 50 °C, the resulting tricyclic ketone is reductively aminated with NH_3 and $NaBH_3CN$ in the presence of $Ti(O\text{-}i\text{-}Pr)_4$ and $TiCl_4$ in EtOH/CH_2Cl_2 to yield a diastereomeric mixture of primary amines that are separated by preparative TLC, providing the 6(*R*)-amine (VII). Finally, amine (VII) is acylated with ethyl chloroformate (VIII) in the presence of Et_3N in CH_2Cl_2 (1, 2). Scheme 1.

In another strategy, *N*-acylation of the tricyclic amino acid (IX) with ethyl chloroformate (VIII) yields the carbamate (X), which, after reduction of the carboxyl group to the corresponding aldehyde (XI), is subjected to Wittig reaction with phosphonate (XII) (3, 4). Scheme 1.

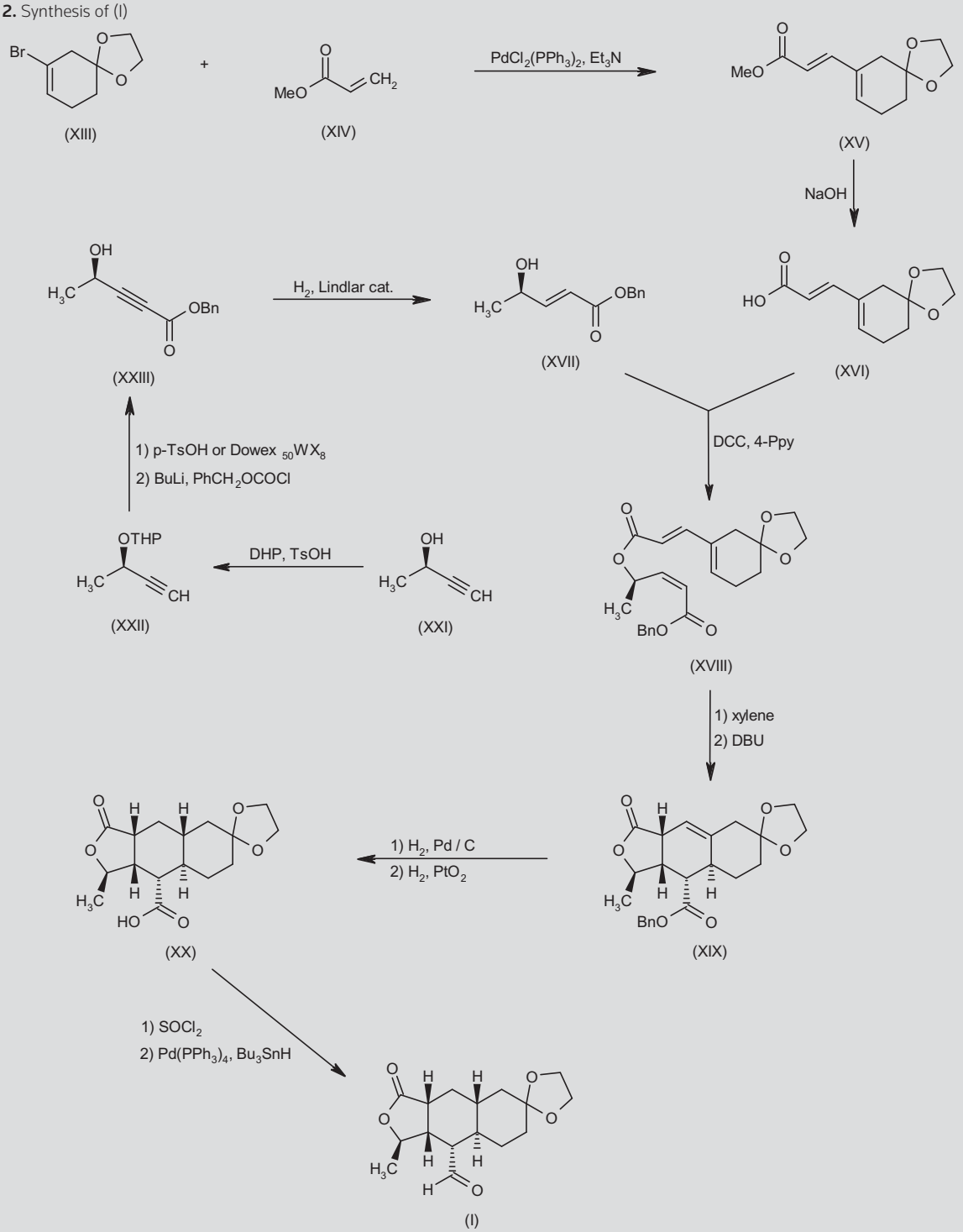
The tetracyclic aldehyde (I) is prepared as follows. Heck coupling of 3-bromo-3-cyclohexen-1-one ethylene ketal (XIII) with methyl acrylate (XIV) in the presence of $PdCl_2(PPh_3)_2$ and Et_3N in DMF at 75 °C gives the dienoate ester (XV), which is hydrolyzed to the corresponding carboxylic acid (XVI) using NaOH in THF/MeOH. Subsequent DCC-mediated coupling of acid (XVI) with alcohol (XVII) in the presence of 4-pyrrolidinopyridine (4-Ppy) in CH_2Cl_2 affords the triene ester (XVIII). Intramolecular Diels–Alder reaction in triene (XVIII) by

Scheme 1. Synthesis of Vorapaxar



heating in xylene at 215 °C results in a tetracyclic intermediate, which undergoes epimerization at C9a by means of DBU in THF to provide the *cis*-lactone (XIX). The benzyl ester group of (XIX) is then removed by catalytic hydrogenolysis over Pd/C in EtOAc, and subsequent diastereoselective hydrogenation of the internal double bond over PtO_2 in EtOAc affords the tetracyclic carboxylic acid (XX). Finally, chlorination of acid (XX) with $SOCl_2$ in toluene at 180 °C followed by reduction of the resulting acid chloride with Bu_3SnH in the presence of $Pd(PPh_3)_4$ in toluene yields the key aldehyde (I) (5, 6). Scheme 2.

Scheme 2. Synthesis of (I)



Hydroxy ester (XVII) is obtained by protection of 2(*R*)-butynol (XXI) as the corresponding tetrahydropyranyl ether (XXII) with DHP in the presence of *p*-TsOH. Subsequent deprotonation of the terminal alkyne in compound (XXII) by means of BuLi and treatment with $PhCH_2OCOCl$ in THF at –78 °C followed by acidic THP group hydrolysis yields benzyl ester (XXIII), which is finally submitted to partial reduction of the triple bond by hydrogenation over Lindlar catalyst in THF (5, 6). Scheme 2.

The tricyclic intermediate (IX) can be prepared by two alternative pathways:

Protection of 2(*R*)-butynol (XXI) with HMDS by means of H_2SO_4 in refluxing THF gives the corresponding silyl ether (XXVIII), which, after deprotonation with hexyl lithium, undergoes carbamoylation with 1-(diphenylcarbamoyl)imidazole (XXIX) in THF/toluene, yielding 4(*R*)-hydroxy-*N*,*N*-diphenyl-2-pentynamide (XXX) (3, 4). Alternatively, propargylic alcohol (XXX) is obtained by enzymatic resolution of racemic 4-hydroxy-*N*,*N*-diphenyl-2-pentynamide (XXXI) by means of vinyl acetate in the presence of selected lipase enzymes, producing a mixture of ureacted (*S*)-alcohol and (*R*)-acetate ester, which, after isolation, is hydrolyzed with KOH or with hydrolase enzyme (7). Reduction of propargyl derivative (XXX) with H_2 over Lindlar catalyst in EtOAc affords 4(*R*)-hydroxy-*N*,*N*-diphenyl-2-pentenamide (XXXII), which is then coupled with carboxylic acid (XVI) via the mixed anhydride method or with EDC and DMAP, providing ester (XXXIII). Intramolecular Diels–Alder reaction of triene (XXXIII) in refluxing xylene followed by epimerization by treatment with DBU leads to the decahydronaphtho[2,3-*c*]furan derivative (XXXIV), which by subsequent catalytic hydrogenation over Pt/C in EtOAc yields the saturated compound (XXXV). Finally, hydrolysis of *N*,*N*-diphenylamide (XXXV) with NaOH followed by ketal hydrolysis by means of HCl furnishes the keto acid (XXXVI), which is then reductively aminated to afford intermediate (IX) (3). Scheme 3.

Alternatively, esterification of 3-(5-nitro-1-cyclohexenyl)-2-propenoic acid (XXXVII) with benzyl 4(*R*)-hydroxy-2-pentynoate (XXIII) via the mixed anhydride method gives the corresponding ester (XXXVIII), which by reduction of its alkyne group with H_2 over Lindlar catalyst in toluene yields olefin (XXXIX). Diels–Alder cyclization of triene (XXXIX) in xylene at 150 °C followed by treatment with DBU furnishes the tricyclic nitro intermediate (XL), which is finally reduced with H_2 over Pt/C in EtOAc (4). Scheme 3.

Several alternative pathways are available for the synthesis of intermediate (X):

Hydrolysis of (5,5-ethylenedioxy-1-cyclohexenyl)acrylic acid (XVI) with *p*-TsOH followed by reductive amination with NH_4OAc and $NaBH_3CN$ and *N*-acylation of the obtained amine with ethyl chloroformate (VIII) gives carbamate (XLI) as a racemic mixture, which is resolved by means of chiral HPLC, providing the (*R*)-enantiomer (XLII). Esterification of acid (XLII) with allylic alcohol (XXXII) in the presence of EDC and DMAP in CH_2Cl_2 yields the corresponding ester (XLIII), which by intramolecular Diels–Alder cyclization in xylene at 147 °C followed by epimerization in the presence of DBU furnishes the tricyclic intermediate (XLIV). Catalytic hydrogenation of alkene (XLIV) over Pt/C affords the saturated compound (XLV) (3), which is finally hydrolyzed with NaOH (3, 4). Scheme 4.

Alternatively, condensation of nitro acid (XXXVII) with the hydroxypentynamide (XXX) by means of pivaloyl chloride, NMP and DMAP yields ester (XLVI), which is submitted to partial hydrogenation over Lindlar catalyst poisoned with quinoline to afford triene (XLVII). Thermal Diels–Alder cyclization of compound (XLVII) followed by epimerization in the presence of DBU provides the tricyclic carbamide (XLVIII). Simultaneous nitro group and olefin reduction in compound (XLVIII) by means of H_2 and Pt/C or by transfer hydrogenation with HCOOH and Pd/C leads to the tricyclic amine (XLIX), which is finally acylated with ethyl chloroformate (VIII) to afford the corresponding carbamate (XLV) (4). Scheme 4.

Other synthetic approaches to intermediate (X) include alkaline cleavage of benzothiazolyl ketone (L) (4) and hydrogenation/debenzylation of the unsaturated precursor (LI) over Pt/C (3). Scheme 4.

Synthetic precursors (L) and (LI) are prepared as follows:

Partial hydrogenation of propargylic ester (LII) over Lindlar catalyst deactivated with quinoline in toluene gives the triene compound (LIII), which by intramolecular Diels–Alder reaction in NMP at 145 °C followed by epimerization with DBU yields the tricyclic adduct (LIV). Reduction of the nitro group of intermediate (LIV) by means of H_2 and Pd/C yields amine (LV), which is finally *N*-acylated with ethyl chloroformate (VIII) to afford intermediate (L) (4). Scheme 5.

The condensation of acid (XLII) with benzyl hydroxypentynoate (XXIII) by means of pivaloyl chloride, Et_3N and DMAP yields ester adduct (LVI), which is submitted to partial hydrogenation in the presence of Lindlar catalyst and quinoline to afford trienoate (LVII). Finally, Diels–Alder cyclization of (LVII) and subsequent epimerization with DBU provides the tricyclic lactone (LI) (3). Scheme 5.

Precursor (XXXVII) is prepared by several alternative strategies:

Conjugate addition of acrolein (LVIII) to nitromethane in the presence of KOH in MeOH followed by treatment with $Na_2S_2O_5$ in H_2O gives the nitrodisulfonate (LIX), which is hydrolyzed with glyoxylic acid by means of $NaHCO_3$ to yield 4-nitroheptanedial (LX). Compound (LX) is cyclized in the presence of pyrrolidine and PhCOOH in CH_2Cl_2, providing 5-nitro-1-cyclohexenecarbaldehyde (LXI). Wittig reaction of aldehyde (LXI) with (methoxycarbonylmethylene)triphenylphosphorane (LXII) leads to conjugated ester (LXIII), which is finally saponified with NaOH (4). Scheme 6.

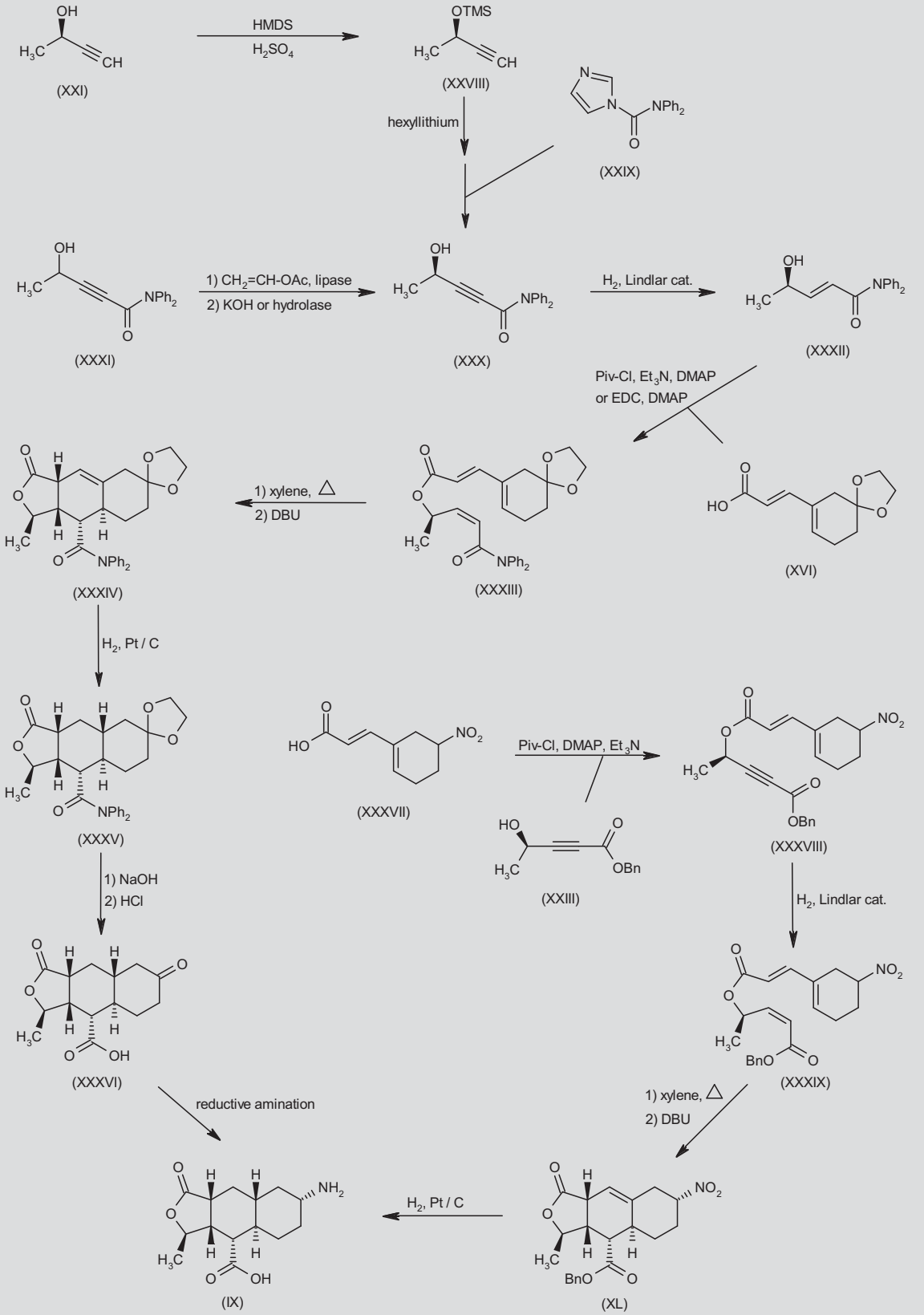
Acid (XXXVII) can be alternatively prepared by Knoevenagel condensation of aldehyde (LXI) with malonic acid (LXIV) (4). Scheme 6.

Hydrolysis of ethylene ketal (XVI) with aqueous *p*-toluenesulfonic acid gives ketone (LXV), which, without isolation, is converted to oxime (LXVI) by addition of hydroxylamine hydrochloride. Subsequent oxidation of oxime (LXVI) using sodium molybdate and H_2O_2 leads to compound (XXXVII) (8). Scheme 6.

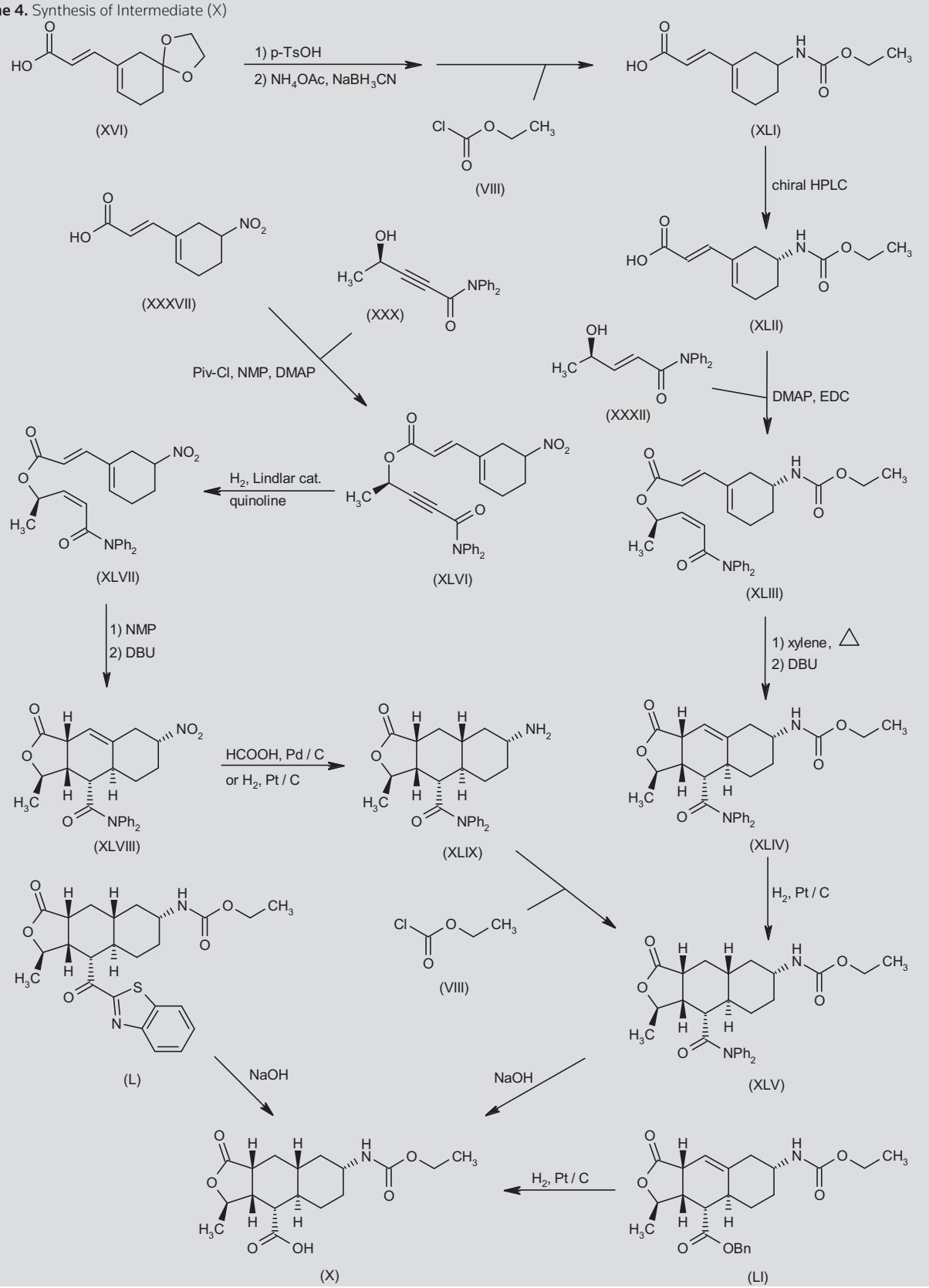
Compounds (II) and (XII) can be prepared as follows:

Rearrangement of 5-bromo-2-methylpyridine 1-oxide (LXVII) with trifluoroacetic anhydride gives (5-bromopyridin-2-yl)methyl trifluoroacetate (LXVIII), which, without isolation, is hydrolyzed in MeOH solution, yielding (5-bromopyridin-2-yl)methanol trifluoroacetate salt (LXIX). Basification of compound (LXIX) with K_2CO_3 followed by chlorination with $SOCl_2$ affords 5-bromo-2-(chloromethyl)pyridine (LXX), which is subsequently condensed

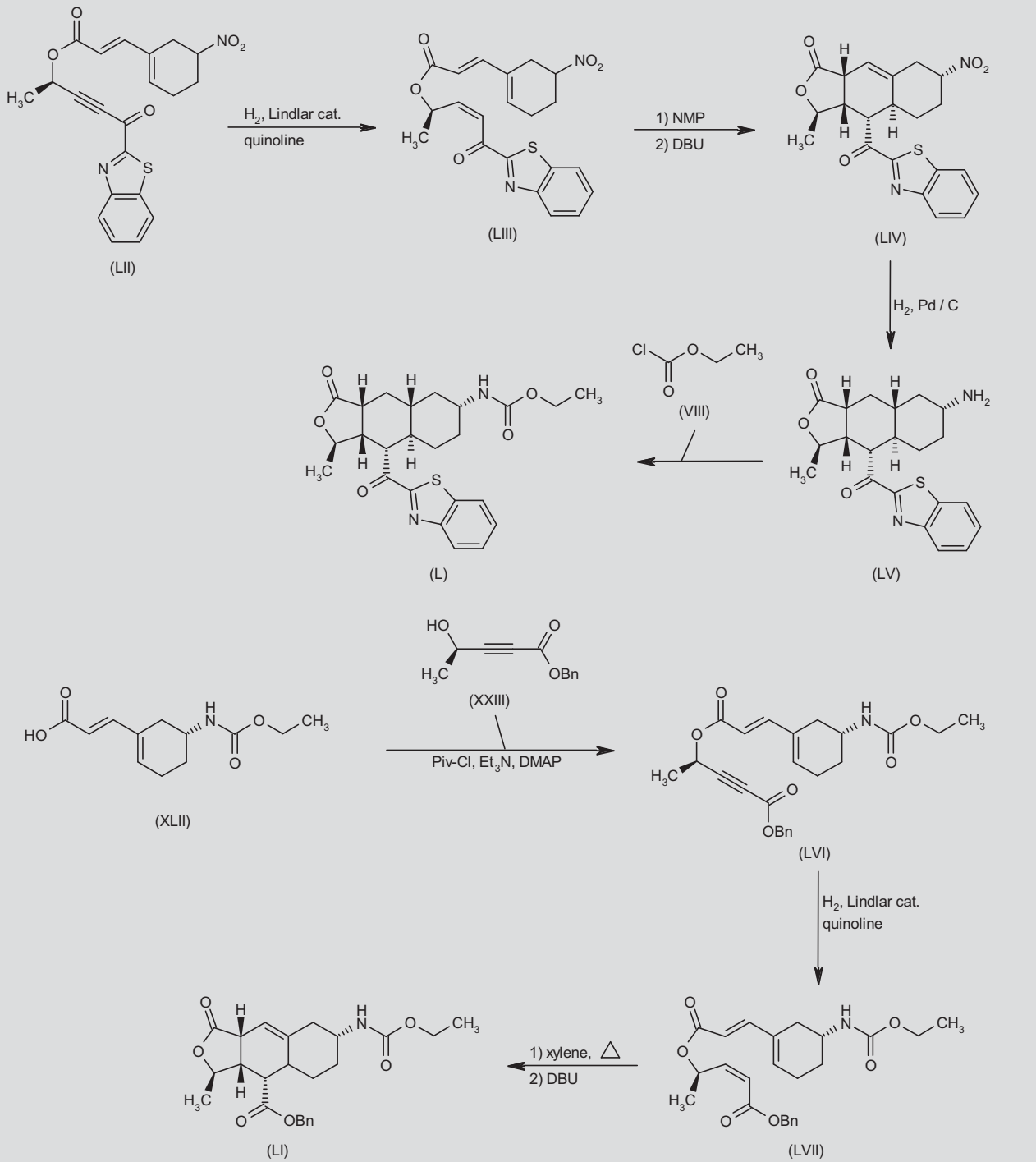
Scheme 3. Synthesis of Intermediate (IX)



Scheme 4. Synthesis of Intermediate (X)



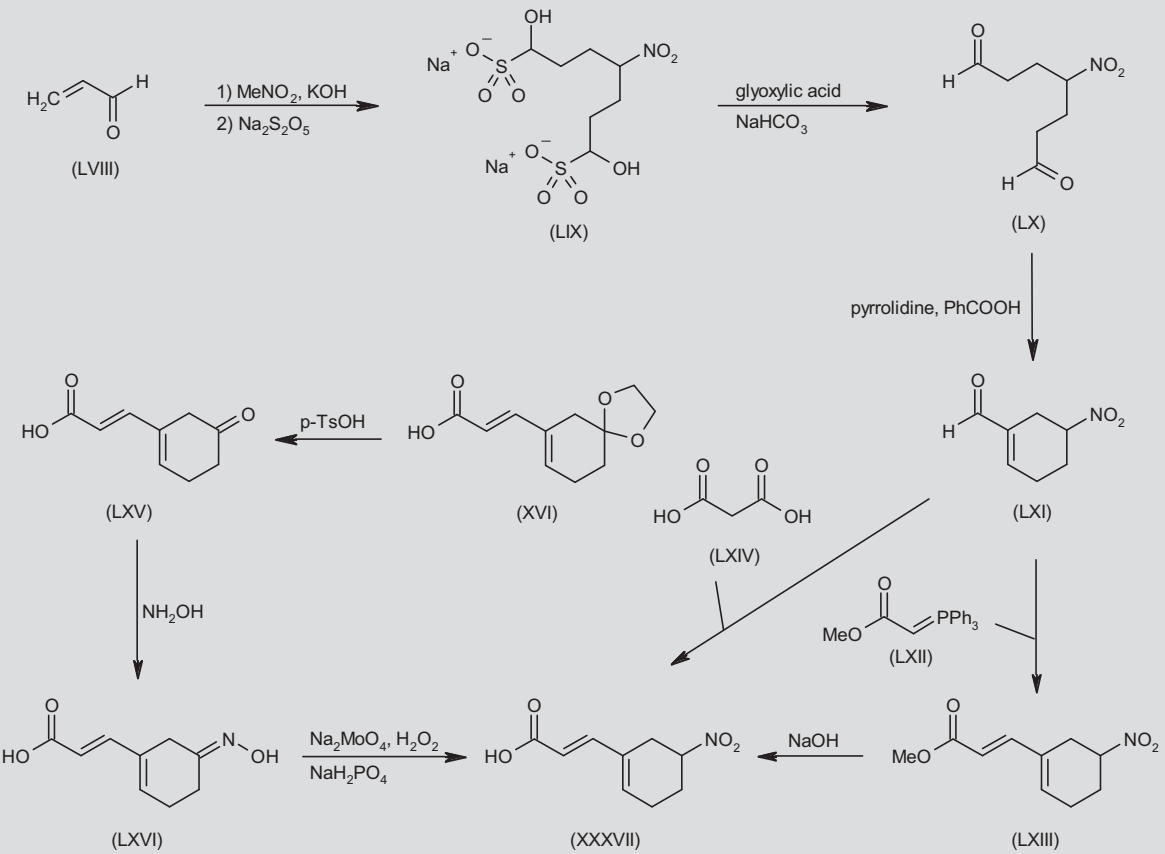
Scheme 5. Synthesis of Precursors (L) and (LI)



with diethyl phosphite in the presence of LiHMDS, affording phosphonate (LXXI). Finally, Suzuki coupling of bromopyridine derivative (LXXI) with 3-fluorophenylboronic acid (V) by means of Na_2CO_3 and Pd/C in H_2O at 75 °C provides the phenylpyridine compound (XII) (4). Scheme 7.

O-Protection of 6-methyl-3-pyridinol (LXXII) with TIPSCl in DMF gives the corresponding silyl ether (LXXIII), which is then condensed with diethyl chlorophosphate (LXXIV) in the presence of BuLi and DIEA in THF, yielding diethyl phosphonate (II) (1). Scheme 7.

Scheme 6. Synthesis of Precursor (XXXVII)



BACKGROUND

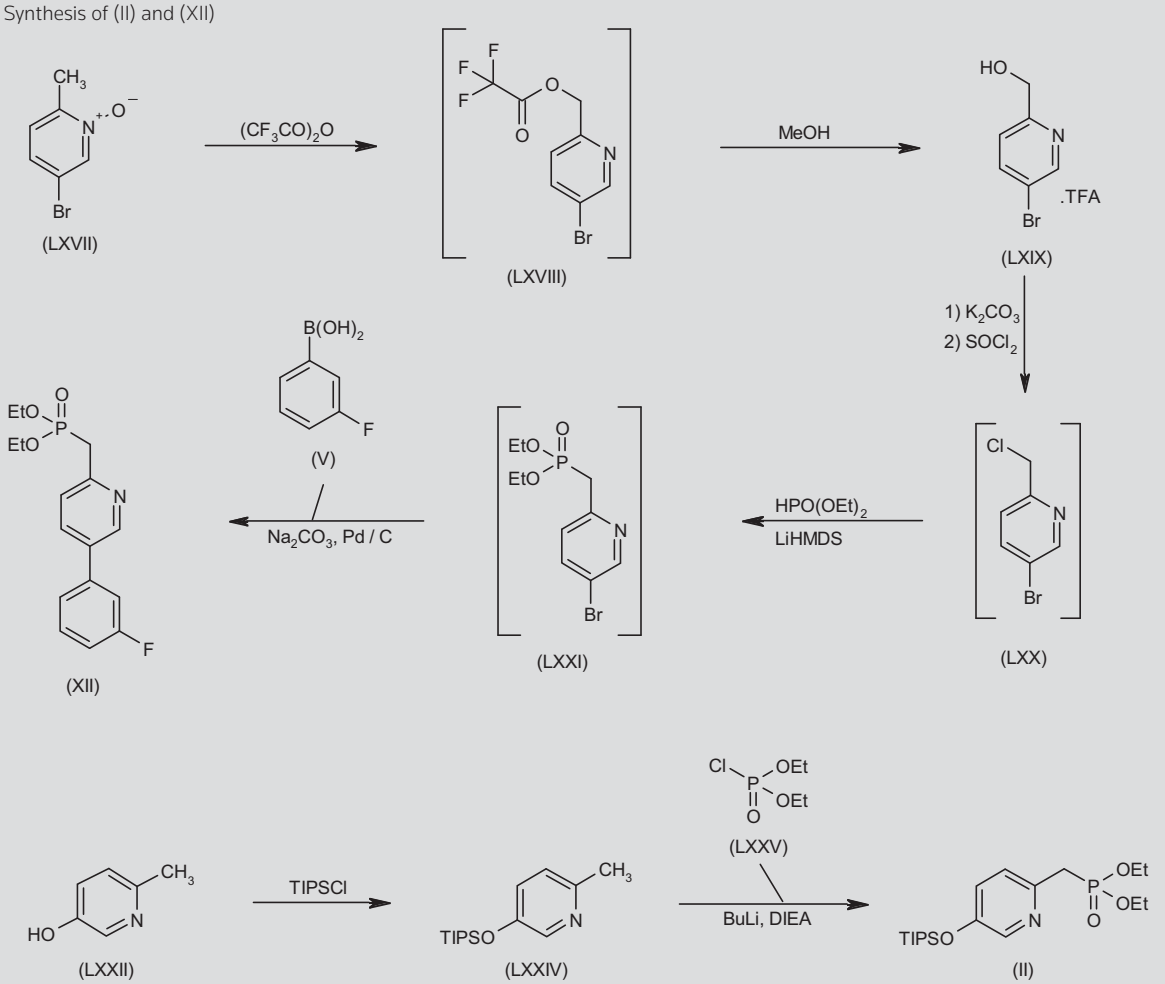
Antiplatelet therapy has proven effective in the prevention of atherothrombotic events, including myocardial infarction and ischemic stroke (9, 10). Indeed, aspirin and clopidogrel are commonly prescribed drugs throughout the world. Numerous clinical trials have clearly demonstrated that the risk of atherothrombotic events can be reduced with the use of antiplatelet therapy, including aspirin, ticlopidine and clopidogrel (9-11). Despite these obvious advantages, the indication for antiplatelet therapy is limited predominantly to high-risk patients, mostly due to the increased risk of bleeding complications (9, 12, 13). Indeed, an increased risk of bleeding associated with the use of antiplatelet therapy is not only a logical consequence of the nature of antiplatelet therapy (14), but also a proven fact documented by many clinical studies (9, 12, 15, 16).

Thrombotic ischemic events must be prevented, since they often lead to catastrophic outcomes such as heart failure, disability due to ischemic stroke, or even death. On the other hand, bleeding complications due to excess use of antiplatelet agents should also be avoided because they cause serious outcomes, such as disability due to hemorrhagic stroke, or even hemorrhagic fatalities (13, 17). Moreover, even minor bleeding events are harmful for patients because the risk of thrombotic ischemic events may be increased due to reduced compliance to antiplatelet agents in patients with frequent bleeding episodes (18).

Future antiplatelet strategies should ideally be directed towards the "reduction of thrombotic events without increasing the risk of bleeding events". Recently published registry studies from "real life" experiences clearly demonstrate that approximately 4% of patients with or at high risk of atherothrombosis experience cardiovascular death, myocardial infarction or stroke (19-21), although more than 70% of them were adequately treated by currently available antiplatelet therapy (22).

Congenital deficiency of platelet GPIIb/IIIa (Glanzmann's thrombasthenia) results in the absence of platelet aggregation (23). Patients with Glanzmann's thrombasthenia are at high risk of bleeding, but minimum risk of thrombotic events. Thus, with the use of antiplatelet agents to block the function of the GPIIb/IIIa receptor (anti-GPIIb/IIIa agents), platelet-mediated thrombotic events were expected to be prevented by inhibiting platelet aggregation (24). Indeed, when used after coronary intervention, i.v. administration of anti-GPIIb/IIIa agents prevented thrombotic complications (25). However, the use of anti-GPIIb/IIIa agents did not work for secondary or primary prevention of thrombotic diseases, because the reduction in thrombotic events can be achieved only with a substantial increase in the risk of bleeding complications (24, 26). Several

Scheme 7. Synthesis of (II) and (XII)



clinical trials with the use of orally available anti-GPIIb/IIIa agents, which still inhibit platelet aggregation, demonstrated minimal reduction of thrombotic events with a substantial increase in bleeding complications (24). With the experience of these anti-GPIIb/IIIa agents, we clearly recognize that the overall benefit of antiplatelet therapy should be assessed as the balance between an increased risk of bleeding and a reduced risk of thrombotic events (14).

Clopidogrel is now largely used worldwide (27) both as monotherapy (prevention of atherothrombosis) (11, 28) and in combination with aspirin for acute coronary syndromes (15). The spread of clopidogrel use is based on a clinical trial performed in the mid-1990s, known as CAPRIE (11). In this trial, patients with coronary artery disease (CAD), cerebrovascular disease (CVD) and peripheral artery disease (PAD) were randomly assigned to either 300 mg/day aspirin or 75 mg/day clopidogrel. This study demonstrated that patients on clopidogrel experienced fewer thrombotic events (cardiovascular death/myocardial infarction/stroke). It is important to note that serious bleeding events in patients receiving clopidogrel were lower than in the aspirin group. This somewhat surprising finding may be due to the extra risk of gastrointestinal bleeding in patients treated with aspirin (29).

In 2001, the molecular target of the active metabolite of clopidogrel, the $P2Y_{12}$ receptor, was cloned (30). Based on the experience in CAPRIE, it was hypothesized that $P2Y_{12}$ receptor antagonism resulted in more efficient prevention of thrombotic events with less bleeding complications than blockade of the arachidonic acid pathway, which is achieved by aspirin. However, recent progress in basic science has revealed that the story is not so linear or simple. Production of the active metabolite of clopidogel varies among patients, which results in heterogeneity of $P2Y_{12}$ receptor antagonism in patients taking 75 mg/day of clopidogrel, as well as substantial differences in response (31). Since the antithrombotic effects of clopidogrel depend on the extent of $P2Y_{12}$ receptor antagonism, variability in production of active metabolites of clopidogrel results in variability in antiplatelet effects. Accordingly, the antiplatelet effect is stronger in some patients (subpopulation at lower risk of thrombosis, but with a higher risk of bleeding), but weaker (subpopulation at higher risk of thrombosis, but with a lower risk of bleeding) in others, although they take the same dosage of clopidogrel. In the CAPRIE study, 75 mg/day clopidogrel proved to be safe and effective compared to 300 mg/day aspirin overall. However, the results indi-

cate a mixture of patients with higher and lower $P2Y_{12}$ receptor antagonism, as shown in Table I.

Recent clinical trials with newer-generation $P2Y_{12}$ receptor antagonists (prasugrel and ticagrelor) with relatively homogeneous $P2Y_{12}$ receptor antagonism revealed an increased incidence of serious bleeding events in the population of patients exposed to homogeneous stronger $P2Y_{12}$ inhibition (17, 32). Indeed, the efficacy and safety of the newer-generation $P2Y_{12}$ receptor antagonists prasugrel and ticagrelor were tested in comparison with current standard-of-care therapy with aspirin/clopidogrel in patients with acute coronary syndrome (15, 30). Both agents were shown to reduce the risk of thrombotic cardiovascular death, myocardial infarction and stroke. However, the risk of serious non-coronary bypass graft surgery (CABG)-related bleeding complications was higher with the use of new-generation $P2Y_{12}$ receptor antagonists. In short, the $P2Y_{12}$ receptor is a safer antiplatelet target than GPIIb/IIIa, although obviously not ideal.

Thrombin is established as the most potent activator of platelets (33, 34). There are several thrombin receptors on human platelets (34, 35), one of which, the protease-activated receptor (PAR), has unique biological properties (36). Thrombin is a serine protease that catalyzes PARs to express their ligands. Importantly, PARs contain their specific ligands within the molecular structure of the receptors themselves (36). Since thrombin is an extremely strong stimulator of platelet activation, a serious increase in bleeding risk was expected when thrombin receptor knockout mice were used as an experimental model. However, it is important to note that there were almost no specific phenotypes in mice deficient in PARs with regard to bleeding (37). It is still uncertain why serious bleeding complications did not increase in mice deficient in PARs. However, the finding that bleeding complications did not increase in PAR-deficient mice, while platelet aggregation induced by thrombin was profoundly blocked, indicated that PARs might be a suitable antiplatelet target for preventing thrombotic events, without increasing the risk of bleeding.

In the physiological setting, thrombin generation occurs predominantly on the surface of activated platelets (38) rather than in plasma, because activated coagulation factors can easily be diluted by the impact of blood flow (39). Local activation of platelets by thrombin generation and further activation of platelets by thrombin receptor stimulation may cause positive feedback to immediately stop bleeding (38).

There is species-dependent heterogeneity for the relative importance of various PARs. In mice, PAR4 is the major ligand for platelet activation, while in humans, PAR1 is the major player in the thrombin-dependent platelet activation pathway (40-43). Thus, PAR1 was selected as a possible target for newer-generation antiplatelet agents.

Vorapaxar (Sch-530348) is a specific antagonist of the platelet PAR1 receptor (1, 44, 45). Vorapaxar is a synthetic tricyclic 3-phenylpyridine analogue of himbacine, a natural product that has been modified as a crystalline salt for drug development and clinical use (46, 47). It is a potent and competitive antagonist of the PAR1 receptor (K_i = 2.7 nmol/L), blocking thrombin-mediated platelet activation without interfering with the cleavage of fibrinogen, the final step in coagulation, which is also provided by thrombin. Vorapaxar is highly selective for PAR1, without affecting other platelet receptors or pathways involved in platelets (1, 45, 48).

Table I. *Outcome of clopidogrel intervention considering the interindividual variability of antiplatelet effects.*

	Thrombotic risk (%/year)	Bleeding risk (%/year)
Control	X	Y
Group A (A%)	0.5xX	2xY
Group B (B%)	0.8xX	1.5xY
Group C (C%)	X	Y
Total population (A+B+C = 100%)	(0.5xA+0.8xB+C)/100xX	(2xA+1.5xB+C)/100xY

The efficacy and safety of the antiplatelet intervention were evaluated in randomized clinical trials with large numbers of patients. In the real world, the risk of thrombotic events without drug intervention (X [%/year]) and the risk of bleeding events without drug intervention (Y [%/year]) vary among patient subpopulations. Randomized trials are conducted under the supposition that the interpatient variability is not very large. At the time of the CAPRIE study, it was reasonable that the interpatient variability of the response with the use of clopidogrel was minimum because the molecular target of clopidogrel had not been identified. However, recent progress in basic science revealed that the pharmacological effects of clopidogrel are not homogeneous for each patient. In the table, we hypothesize three categories of patients with the same dosage of clopidogrel: group A, hyperresponders (50% thrombotic risk reduction with a 2 times increased risk of bleeding); group B, intermediate responders (20% thrombotic risk reduction with a 1.5 times increased risk of bleeding); and group C, nonresponders (no change in thrombotic events with no increase in bleeding complications). We now understand that the overall favorable results of CAPRIE for clopidogrel can be applicable only for a selected population of patients, which has not yet been clarified.

PRECLINICAL PHARMACOLOGY

Preclinical studies performed in nonhuman primates revealed that vorapaxar at a dose of 0.1 mg/kg p.o. completely inhibited platelet aggregation for 24 hours (1, 45). Details of the pharmacodynamic and pharmacokinetic aspects of vorapaxar in these animals have been published elsewhere (1). It is important to note that inhibition of platelet aggregation lasts for more than 24 hours even though plasma concentrations of the drug decreased to below 2.5 ng/mL. Similar prolonged inhibitory effects on platelet aggregation were demonstrated in human blood specimens as well (45).

Similar to other antiplatelet agents, the clinical development of vorapaxar began with a phase I study in healthy volunteers. The first study in humans performed with orally administered vorapaxar demonstrated inhibition of thrombin-induced and thrombin receptor-activating peptide (TRAP)-induced platelet aggregation with IC_{50} values of 47 and 25 nM, respectively. This agent is specific for PAR1 and does not influence ADP receptors, because the aggregation obtained by ADP, the TXA_2 mimetic U-46619 or collagen was not affected. Moreover, it did not affect prothrombin time or activated partial thromboplastin time, suggesting the safety of the drug in terms of bleeding risk (1).

PHARMACOKINETICS AND METABOLISM

Following oral administration, the drug is rapidly absorbed, metabolized and eliminated predominantly by the biliary and gastrointestinal routes. Less than 5% of the drug is eliminated via the kidney. The terminal half-life ($t_{1/2}$) is estimated to be 126-269 hours. The

binding of vorpaxar to PAR1 is reversible; however, the dissociation kinetics of vorapaxar from its receptor are slow. These specific characteristics of vorapaxar may explain its long $t_{1/2}$ (1).

SAFETY

The safety profile of vorapaxar was evaluated in three multicenter, randomized, double-blind, placebo-controlled, dose-ranging phase II clinical trials. The largest study, named Thrombin Receptor Antagonist for Cardiovascular Event Reduction in Percutaneous Coronary Intervention (TRA-PCI), was conducted in the U.S. In this study, 1,030 stable CAD patients were recruited from 76 centers around the country (49). Patients were randomly assigned to vorapaxar or placebo in a 3:1 ratio, in addition to standard-of-care antithrombotic therapy. In patients assigned to the drug treatment arm (n = 773), one of three single loading doses of vorapaxar (10, 20 or 40 mg) was administered before angiography. Finally, patients undergoing percutaneous coronary intervention (PCI; n = 573) received maintenance therapy with one of three doses (0.5, 1 and 2.5 mg) of vorapaxar for 2 months. No differences were observed in terms of TIMI major bleeding, minor bleeding and the composite major plus minor bleeding for vorapaxar (with all loading and maintenance doses) versus placebo. Moreover, this study revealed a strong trend towards a lower rate of deaths and major adverse cardiac events, including myocardial infarction, in vorapaxar arms as compared to the placebo arm. Although this study was focused on the safety profile and not adequately powered to evaluate efficacy, it provided sufficient evidence in order to prepare larger phase III trials.

The safety profile of vorapaxar was later confirmed by two relatively small sample size studies focusing on different patient populations and treatment durations. Both were conducted in Japan. In the first, a total of 117 patients undergoing PCI for a non-ST elevation acute coronary syndrome were randomized to vorapaxar for 60 days (20- or 40-mg loading dose followed by 1- or 2.5-mg maintenance dose) or placebo added to standard-of-care antithrombotic therapy. Of note, all the patients who underwent PCI received both aspirin and ticlopidine. No differences were observed with regard to the primary safety endpoint (TIMI major and minor bleeding). Similar to the U.S. study, there was a strong trend for fewer non-fatal myocardial infarctions in the vorapaxar arm. In fact, there was a statistically significant difference between vorapaxar and controls, although the sample size was too small to reach any definite conclusion in terms of efficacy (50).

In the second Japanese study, the safety of vorapaxar was assessed in the setting of patients with previous ischemic stroke in combination with aspirin in a 1:1:1 randomized fashion with vorapaxar 1 or 2.5 mg/day for 60 days or placebo. The sample size for this study was 90 in total, but the results were meaningful because most of the patients enrolled had a history of lacunar stroke, which has a high risk for intracranial bleeding. However, no intracranial bleeding was detected in patients treated with vorapaxar. Neither TIMI major nor TIMI minor bleeding was detected in vorapaxar-treated patients (51). The results of both studies confirm that vorapaxar is well tolerated and suggest a reasonable safety profile for the novel PAR1 receptor antagonist.

CLINICAL STUDIES

Two phase III studies are currently going. One is designed to compare vorapaxar to placebo in addition to standard of care in patients for secondary prevention of atherothrombosis. The details of the study design have been published elsewhere (52). Briefly, the TRA2P-TIMI 50 trial (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events) will assess the effects of vorapaxar (2.5 mg once daily as maintenance dose for at least 1 year) on secondary prevention in patients with a known history of CAD, PAD and CVD. The primary efficacy endpoint of the study is the first occurrence of any component of the composite of cardiovascular death, myocardial infarction, stroke and urgent coronary revascularization.

Another phase III study is being conducted to evaluate the effects of vorapaxar in patients with acute coronary syndrome. The detailed study design was published elsewhere (46). In the ongoing TRA-CER trial (Thrombin Receptor Antagonist for Clinical Event Reduction in ACS), the impact of vorapaxar combined with standard of care (aspirin plus clopidogrel) in the prevention of recurrent ischemic events is being assessed (53). The primary efficacy endpoint of the study is the first occurrence of any component of the composite of cardiovascular death, myocardial infarction, stroke, recurrent ischemia with rehospitalization and urgent coronary revascularization. The TRA-CER study will evaluate a 40-mg loading dose and a 2.5-mg maintenance dose of vorapaxar in approximately 10,000 patients with acute coronary syndrome for > 1 year of follow-up.

CONCLUSIONS AND FUTURE PERSPECTIVES

The PAR1 receptor may be a better target for antiplatelet therapy due to the more optimal balance between antithrombotic effects and increased risk of bleeding complications compared to the $P2Y_{12}$ receptor. Evidence from human studies supports the hypothesis that PAR1 receptor antagonism is safe with regard to bleeding complications, although careful consideration is necessary in patients with a previous history of stroke. Ongoing phase III trials are designed to demonstrate the efficacy and safety of vorapaxar in the prevention of thrombotic events in patients with atherothrombosis in general, except for patients with a previous history of stroke, while the trial in patients with acute coronary syndromes has been terminated. Detailed clarification of the role of PAR1 in triggering the onset of thrombotic events in humans is also expected to be better defined by the experimental research with vorapaxar.

SOURCE

Merck & Co., Inc. (US).

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Dr. Goto has received consulting fees/honoraria from Eisai, sanofi-aventis, Otsuka, Daiichi Sankyo and Schering-Plough (now Merck & Co.) of over $10,000 in the last 3 years, as well as a research grant from sanofi-aventis of over $10,000 last year. Dr. Serebruany has received consulting fees/honoraria from sanofi-aventis and Boehringer Ingelheim of over $10,000 in the last 3 years, as well as a research grant from sanofi-aventis, Eisai, Novartis, Pfizer, Abbott and Pronova of over $10,000 last year. Dr. Serebruany is listed as an inventor for the issued U.S. patent: Serebruany, V.L. (HeartDrug Research, LLC). *Treating vascular events with statins by inhibiting PAR-1 and PAR-4*. US 7842716.

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