Contemporary Drug Synthesis

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Preface

Armed with a vast amount of knowledge acquired at school, along with a degree in chemistry, you are starting your career in the pharmaceutical industry. You may be working in medicinal chemistry, process chemistry, or radiochemistry. This new endeavor may seem daunting, especially when you consider that you may need to be proficient in areas in which you have not been prepared. This manuscript will illustrate how chemistry, biology, pharmacokinetics, and a host of other disciplines all come together to produce successful new medicines. In order to achieve that goal, we have compiled a collection of fourteen representative categories of drugs that we have carefully chosen from among the best-selling drugs. We have provided an introduction to each drug including a historical perspective, and background to the biology, pharmacology, pharmacokinetics, and drug metabolism followed by a detailed account of the synthesis. The targeted audience goes beyond individuals new to the pharmaceutical industry; many veterans of the industry may well find something new in this text. There are a few points we felt worth reiterating. For example:

a). The advent of new synthetic methodology enables chemists to synthesize drugs in a more convergent and more efficient fashion, a theme seen over and over again in this monograph. Consequently, literature awareness is essential for the chemist in the pharmaceutical industry.

b). Knowing the history of successful drugs and understanding their attributes is very important and the lessons learned can be applied to current programs in drug discovery. A tremendous amount of knowledge has accumulated over the last few decades. Attributes of a successful drug include appropriate potency, selectivity, bioavailability, and physiochemical properties.

c). Serendipity in the drug industry also plays an important role. On the other hand, opportunity favors prepared minds. Many examples can be found in this manuscript. For example, Viagra®, currently used for erectile dysfunction (ED), was initially developed as a PDE5 inhibitor for hypertension. Likewise, Rogaine®, currently used topically for hair growth, was first synthesized as a potassium channel opener, also for hypertension. Propecia®, currently used orally for hair growth, was originally prepared as a testosterone-5α-reductase inhibitor for the treatment of benign prostatic hyperplasia (BPH). Therefore, one should be cognizant during the clinical trials; even failure for the initially intended therapeutic indication does not necessarily equate the end of a drug as long as it has been proven to be safe.

d). Another point that medicinal chemists often overlook (sometimes justifiably) is that the synthesis of the drug should be eventually amenable to cost-effective scale-up to make it economically viable. This is where process chemists play an important role. In the subsequent chapters, we have incorporated process synthesis routes when the information was available.

We are grateful to Professor David L. Van Vranken at University of California at Irvine, who read the manuscript and offered many valuable comments and suggestions. We are also indebted to Dr. Alan J. Kraker, Dr. Lorna H. Mitchell, Dr. Derek A. Pflum, Dr. Stephen Cho, Larry Bratton, and William C. Patt for proofreading portions of the manuscript.

Jie Jack Li
Douglas S. Johnson

March 2004

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Brand Names and Their Corresponding USANs

Abilify®	aripiprazole
Accutane®	isotretinoin
Advair®	fluticasone propionate and salmeterol xinafoate
Allegra®	fexofenadine
Amerge®	naratriptan hydrochloride
Axert®	almotriptan malate
Celebrex®	celecoxib
Cialis®	tadalafil
Cipro®	ciprofloxacin
Clarinex®	desloratadine
Claritin®	loratadine
Crestor®	rosuvastatin
Finasteride®	finasteride
Flonase®	fluticasone propionate
Flovent®	fluticasone propionate
Frova®	frovatriptan succinate
Geodon®	ziprasidone
Gleevec®	imatinib mesylate
Imitrex®	sumatriptan succinate
Lescol®	fluvastatin
Levitra®	vardenafil hydrochloride
Lipitor®	atorvastatin calcium
Maxalt®	rizatriptan benzoate
Mevacor®	lovastatin
Nexium®	esomeprazole
Paxil®	paroxetine hydrochloride
Plavix®	clopidogrel
Prilosec®	omeprazole
Relpax®	eletriptan hydrobromide
Risperdal®	risperidone
Pravacol®	pravastatin
Prozac®	fluoxetine hydrochloride
Rogaine®	minoxidil

Serevent®	salmeterol xinafoate
Seroquel®	quetiapine fumarate
Singulair®	montelukast sodium
Tazorac®	tazarotene
Ticlid®	ticlopidine
Viagra®	sildenafil citrate
Vioxx®	rofecoxib
Xenical®	orlistat
Zocor®	simvastatin
Zoloft®	sertraline hydrochloride
Zomig®	zolmitriptan
Zyprexa®	olanzapine
Zyrtec®	cetirizine dihydrochloride
Zyvox®	linezolid

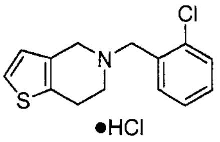
Acronyms and Abbreviations

Ac	acetyl
ADP	adenosine diphosphate
ALIQUAT	tricaprylmethyl ammonium chloride
cAMP	adenosine cyclic 3',5'-phosphate
ATP	adenosine triphosphate
AUC	area under curve
BER	borohydride exchange resin
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BMI	body mass index
Boc	*tert*-butyloxycarbonyl
Bn	benzyl
BPH	benign prostatic hyperplasia
BSTFA	bis(trimethylsilyl)-trifluoroacetamide
t-Bu	*tert*-butyl
CL	total clearance
CL_R	renal clearance
CML	chronic myeloid leukemia
CNS	central nervous system
COX-2	cyclooxygenase II
m-CPBA	*m*-chloroperoxybenzoic acid
CSF	cerebal synovial fluid
5-CT	5-carbamoyltryptamine
CYP	cytochrome
DABCO	1,4-diazabicyclo[2.2.2]octane
DALYS	Disability Adjusted Life Years
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
o-DCB	*o*-dichlorobenzene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DHT	5α-dihydrotestosterone
DNA	deoxy-nucleic acid
ECG	ecocardiograms
ED	erectile dysfunction
EGF	epidermal growth factor
EPS	extrapyramidal side-effects
FDA	Food and Drug Administration
Fen–Phen	fenfluramine and phentermine
GI	gastrointestinal
GISA	glycopeptide-intermediate *S. aureus*

CGMP	cyclic guanosine monophosphate
GPCRs	G-protein-coupled receptors
HMG-CoA	hydroxymethylglutaryl coenzyme A
HMGR	HMG-CoA reductase
HMPA	hexamethylphosphoric triamide
HPL	human pancreatic lipase
HPLC	high-performance liquid chromatography
5-HT	5-hydroxytryptamine (serotonin)
KCO	potassium channel opener
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazane
LTs	leukotrienes
MAO	monoamine oxidase
MDD	major depressive disorder
MICs	minimal inhibition concentrations
MMPP	magnesium monoperoxyphthalate hexahydrate
MOA	mechanism of action
MRSA	methicillin-resistant *Staphylococcus aureus*
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NSAIDs	non-steroidal anti-inflammatory drugs
OA	osteoarthritis
PCC	pyridinium chlorochromate
PDE5	phosphodiesterase-5
PDGFR	platelet-derived growth factor receptor, a kinase
PG	prostaglandin
PK	pharmacokinetics
PKC	protein kinase C
PLE	pig liver esterase
PPH	primary pulmonary hypertension
PPI	proton pump inhibitor
RA	rheumatoid arthritis
Ra-Ni	Raney-Nickel
RCM	ring-closing metathesis
RNA	ribonucleic acid
RT	room temperature
SDAs	serotonin-dopamine antagonists
S_NAr	nucleophilic substitution on an aromatic ring
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
SNRI	serotonin and noradrenaline reuptake inhibition
SPOS	solid phase organic synthesis
SSRI's	selective serotonin reuptake inhibitors
T	testosterone
Tbf	tetrabenzo[*a*,*c*,*g*,*i*]fluorene

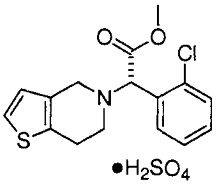
TBS	*tert*-butyldimethylsilyl
TCAs	tricyclic antidepressants
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TKI	tyrosine kinase inhibitor
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMG	tetramethylguanidine
Tol	toluene or tolyl
Ts	tosylate
USAN	United States Adopted Names
UV	ultraviolet
VRE	vancomycin-resistant enterococci
V_{ss}	steady-state volume of distribution

Chapter 1. Antithrombotics:
Ticlopidine (Ticlid®) and Clopidogrel (Plavix®)



1

USAN: Ticlopidine hydrochloride
Trade Name: Ticlid ®
Castaigne S. A.
Launched: 1979
M.W. 263.6



2

USAN: Clopidogrel sulfate
Trade Name: Plavix®
Sanofi/Bristol–Myers Sqibb
Launched: 1993
M.W. 321.8

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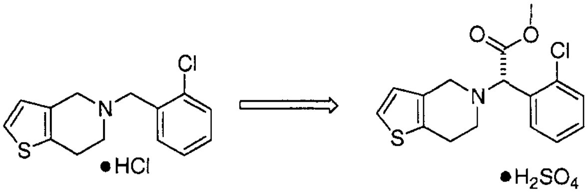
§1.1 Introduction[1-8]



1, Ticlopidine

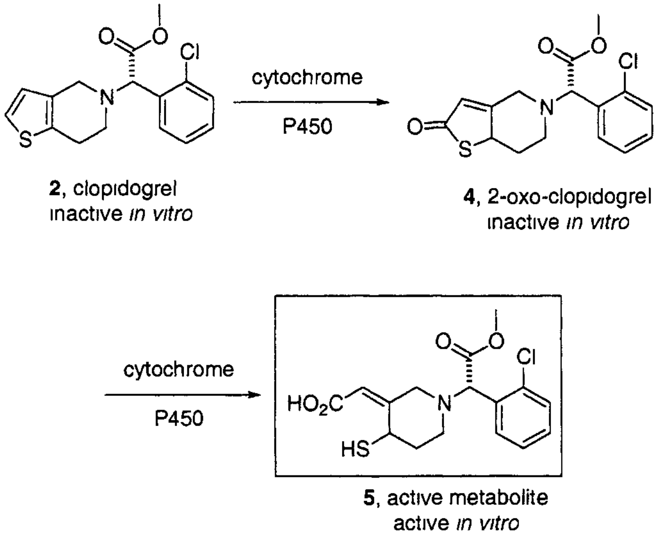
2, Clopidogrel

Fig. 1. Evolution of ticlopidine (**2**) to clopidogrel (**1**).

The process of thrombosis involves the aggregation of platelets, resulting in a pro-coagulation state in the blood that may form a blood clot in the vascolature. Both ticlopidine (**1**) and clopidogrel (**2**) inhibit platelet aggregation induced by adenosine diphosphate (ADP), a platelet activator that is released from red blood cells, activated platelets, and damaged endothelial cells. ADP also induces platelet adhesion. Ticlopidine (**1**) is an older drug, launched in 1979, whereas clopidogrel (**2**), launched in

1993, has achieved with great commercial success. Like its predecessor ticlopidine (**1**), clopidogrel (**2**) is an ADP-dependent platelet aggregation inhibitor. The mechanisms of action for both ticlopidine (**1**) and clopidogrel (**2**) are the same — through the antagonism of the P2Y12 purinergic receptor and prevention of binding of ADP to the P2Y12 receptor. However, both ticlopidine (**1**) and clopidogrel (**2**) are not active *in vitro*, but are activated *in vivo* by cytochrome P450-mediated hepatic metabolism. Remarkably, the identity of the active metabolite **5** of clopidogrel (**2**) was unknown until 1999,[9] when it was isolated after exposure of clopidogrel (**2**) or 2-oxo-clopidogrel (**4**) to human hepatic microsomes. It is noteworthy that ticlopidine (**1**) and clopidogrel (**2**) do not share a common active metabolite.

Due to the aforementioned metabolic activation, an induction period is required for the metabolism-based threshold buildup when patients start to take clopidogrel (**2**); therefore, it may take some time for the effect to manifest.



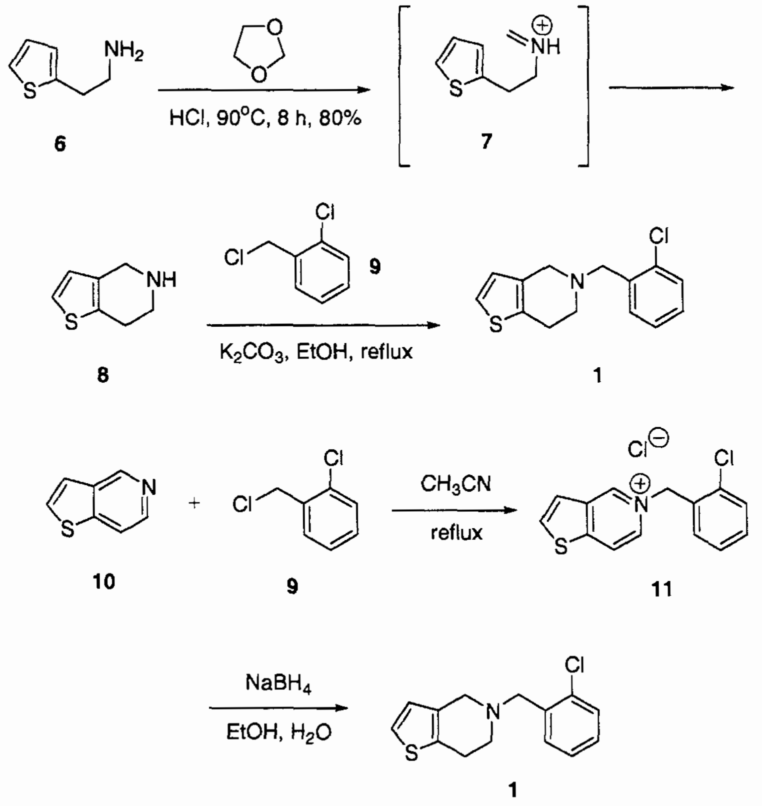
2, clopidogrel
inactive *in vitro*

4, 2-oxo-clopidogrel
inactive *in vitro*

5, active metabolite
active *in vitro*

Fig. 2. *In vivo* metabolism of clopidogrel (**1**).

§1.2 Syntheses of ticlopidine (1)[10–12]

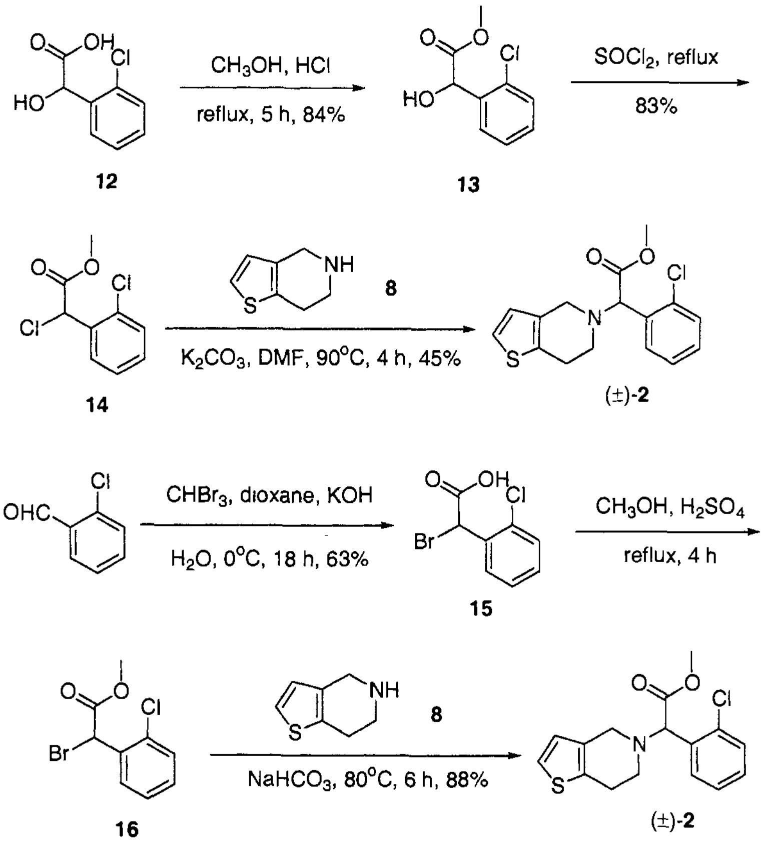


Scheme 1. Synthesis of ticlopidine (**1**).

In one route, ticlopidine (**1**) was assembled *via* S_N2 displacement of 2-chlorobenzyl chloride (**9**) with 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine (**8**).[10,11] The nucleophile **8** was synthesized by heating 2-thiophen-2-yl-ethylamine (**6**) with 1,3-dioxolane in the presence of concentrated hydrochloric acid.[12] 1,3-Dioxolone gave better yields than with formaldehyde, paraformaldehyde and 1,3,5-trioxane. The interesting transformation **6** → **8** first involved the formation of the corresponding Mannich base **7**, which then underwent a Pictet–Spengler type reaction to afford the ring-closure product **8**. It was of interest to note that a possible intramolecular aminomethylation did not take place.

Another route toward ticlopidine (**1**) involved an S_N2 displacement of 2-chlorobenzyl chloride (**9**) by thieno[3,2-*c*]pyridine (**10**) to produce thieno[3,2-*c*]pyridinium chloride **11**. Subsequent reduction of the pyridinium salt (**11**) using $NaBH_4$ then delivered ticlopidine (**1**).[12]

§1.3 Syntheses of Clopidogrel (2)[13–19]



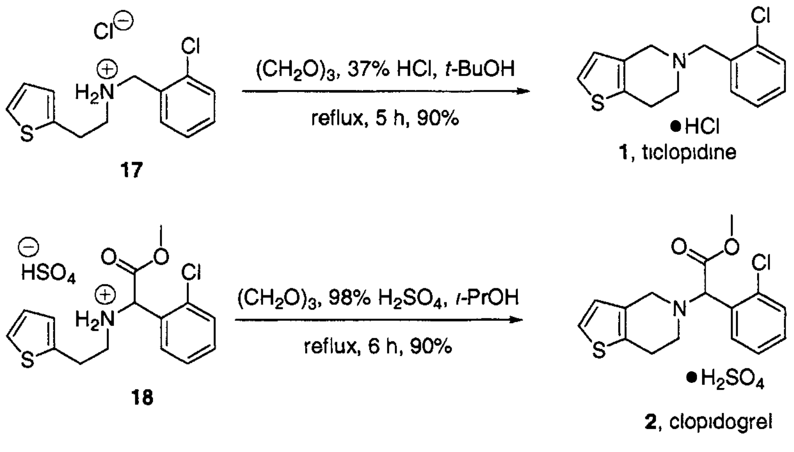
Scheme 2. The Sanofi syntheses of racemic (±)-clopidogrel (**2**).

The original Sanofi synthesis of (±)-clopidogrel (**2**) began with the formation of the methyl ester **13**. Thus methyl mandelate **13** was prepared by refluxing chlorinated mandelic acid **12** with methanol in the presence of concentrated HCl.[13] Chlorination of

13 using thionyl chloride gave methyl α-chloro-(2-chlorophenyl)acetate (**14**). S_N2 displacement of **14** with thieno[3,2-*c*]pyridine (**8**) then delivered (±)-clopidogrel (**2**).

Alternatively, α-bromo-(2-chlorophenyl)acetic acid (**15**) was prepared by treatment of 2-chlorobenzaldehyde with tribromomethane in dioxane with an aqueous solution of potassium hydroxide.[14] Formation of methyl ester **16** was followed by an S_N2 displacement by thieno[3,2-*c*]pyridine (**8**) to afford) an 88% yield of (±)-clopidogrel (**2** in two steps.

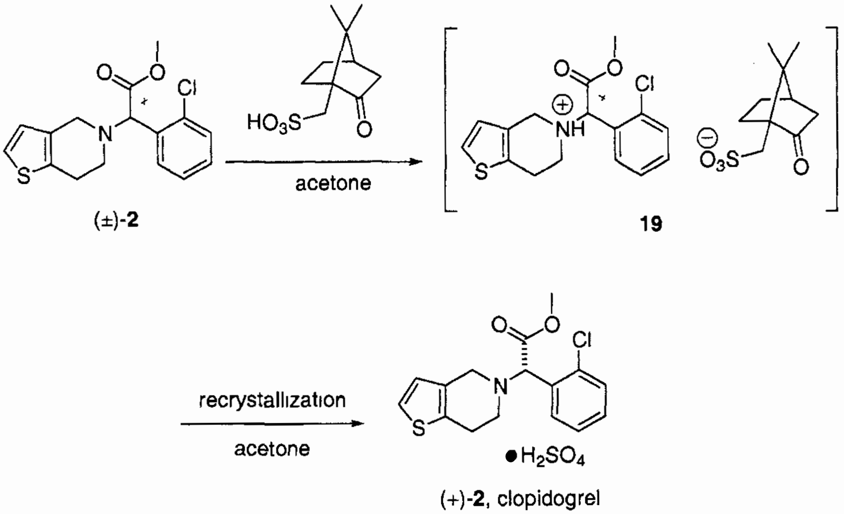
One of the disadvantages of the synthetic route delineated in Scheme 1 is the use of 2-thiophen-2-yl-ethylamine (**6**), whose preparation was not only difficult, but also expensive. Recently, RPG Life Science revealed their one-pot synthesis of ticlopidine and (±)-clopidogrel that did not require the use of 2-thiophen-2-yl-ethylamine (**6**).[15] (2-Chlorobenzyl)-(2-thiophen-2-yl-ethyl)-amine hydrochloride (**17**) was prepared according to US 4127580 and US 5204469. Refluxing **17** with paraformaldehyde in *tert*-butanol with the aid of 37% concentrated HCl gave ticlopidine (**1**). Likewise, refluxing **18** with paraformaldehyde in *iso*-propanol with the aid of 37% concentrated HCl gave (±)-clopidogrel (**2**).



Scheme 3. The RPG synthesis of ticlopidine (**1**) and (±)-clopidogrel (**2**).

Interestingly, only the enantiomerically pure (+)-clopidogrel (**2**) exhibits platelet aggregation inhibiting activity, while the (−)-(**2**) is inactive.[16] Moreover, the inactive (−)-

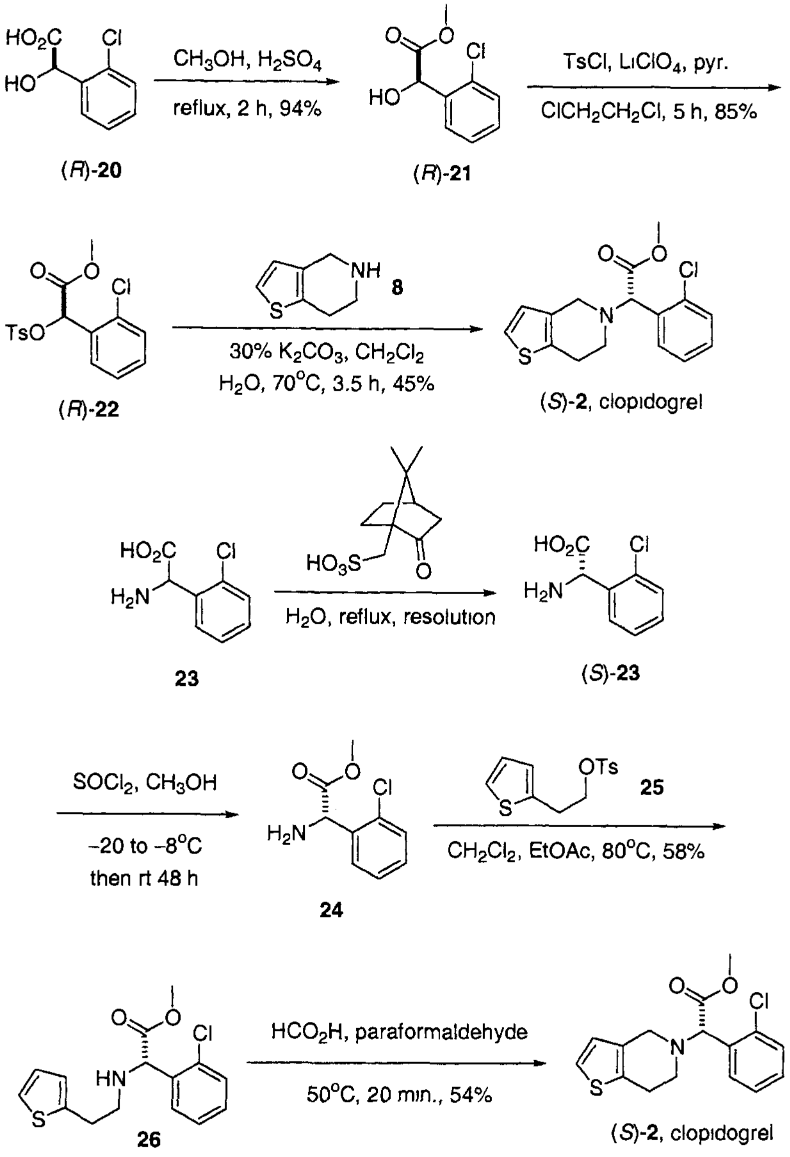
(**2**) isomer is 40 times less well tolerated between the two enantiomers. Therefore, it is evidently advantageous to administer (+)-clopidogrel (**2**). With regard to the enantiomerically pure (+)-clopidogrel (**2**), it was originally obtained from resolution of the racemic clopidogrel (**2**) or through intermediates that were derived *via* resolution. For instance,[17] racemic clopidogrel (**2**) was treated with levorotary camphor-10-sulfonic acid in acetone to afford a salt **19**, which was recrystallized from acetone to generate (+)-clopidogrel (**2**).



Scheme 4. The Sanofi synthesis of enantiomerically pure (+)-clopidogrel (**2**).

One Sanofi synthesis of enantiomerically pure (+)-clopidogrel (**2**) utilized optically pure (*R*)-(2-chloro-phenyl)-hydroxy-acetic acid (**20**), a mandelic acid derivative, available from a chiral pool.[18] After formation of methyl ester **21**, tosylation of (*R*)-**21** using toluene sulfonyl chloride led to α-tolenesulfonate ester **22**. Subsequently, the S_N2 displacement of **22** with thieno[3,2-*c*]pyridine (**8**) then constructed (+)-clopidogrel (**2**). Another Sanofi synthesis of enantiomerically pure (+)-clopidogrel (**2**) took advantage of resolution of racemic α-amino acid **23** to access (*S*)-**23**.[19] The methyl ester **24** was prepared by treatment of (*S*)-**23** with thionyl chloride and methanol. Subsequent S_N2 displacement of (2-thienyl)-ethyl *para*-toluene-sulfonate (**25**) assembled amine **26**.

Finally, ring-closure was achieved by heating **26** with paraformaldehyde in formic acid at reflux to give (+)-clopidogrel (**2**).



Scheme 5. Asymmetric synthesis of (+)-clopidogrel (**2**).