5. Block

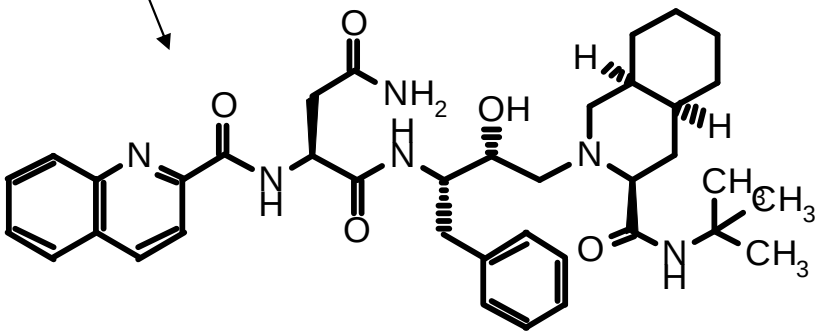
Web Resourses

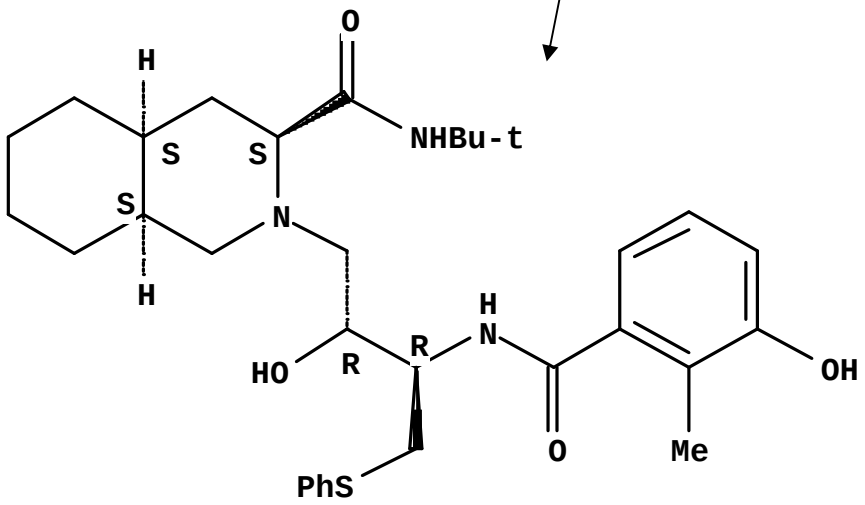
- **http://www.thebody.com/treatment.htm**

- **Look for: Protease inhibitors**

Protease Inhibitors

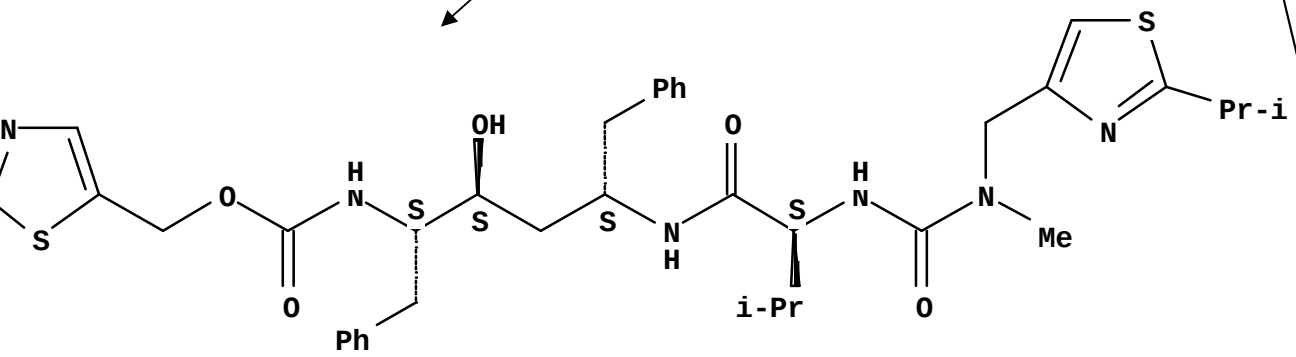
Invirase™ Roche saquinavir	Norvir™ Abbott ritonavir	Crixivan® Merck indinavir	Viracept® Agouron nelfinavir

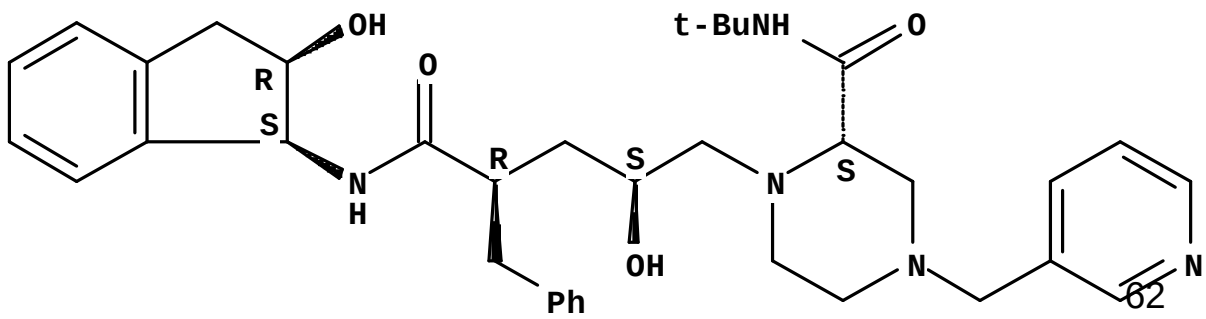




Protease Inhibitors 2

Invirase™ Roche **saquinavir**	**Norvir™** **Abbott** **ritonavir**	**Crixivan®** **Merck** **indinavir**	**Viracept® Agouron** **nelfinavir**





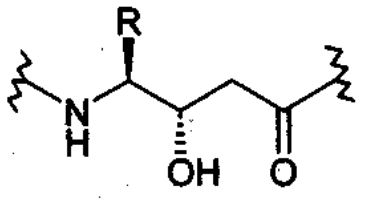
Case Studies 2

Die Identifizierung des HIV- Proteasehemmers Saquinavir

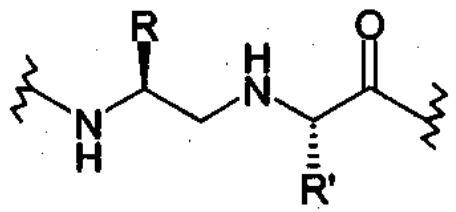
Enzyme Transition State Stabilization

- http://tutor.lscf.ucsb.edu/instdev/sears/biochemistry/tw-enz/enzyme-transition-flash.htm

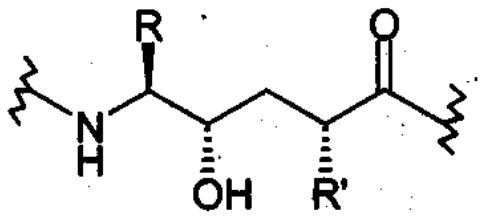
HIV – Protease-Hemmer



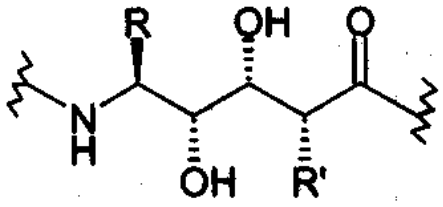
statin



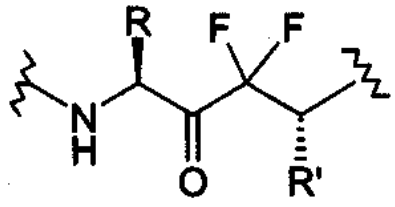
reduced amide



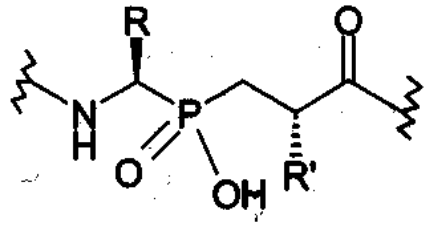
hydroxyethylene



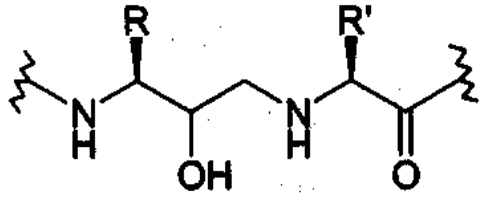
dihydroxyethylene



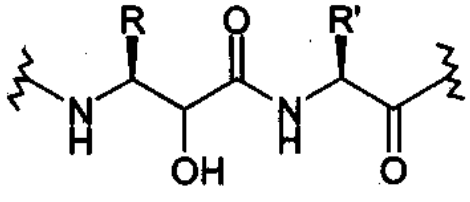
difluoroketone



phosphinic acid



hydroxyethylamine



hydroxymethylcarbonyl

Figure 1 *Transition state mimetics for aspartyl proteases*

HIV – Protease-Hemmer

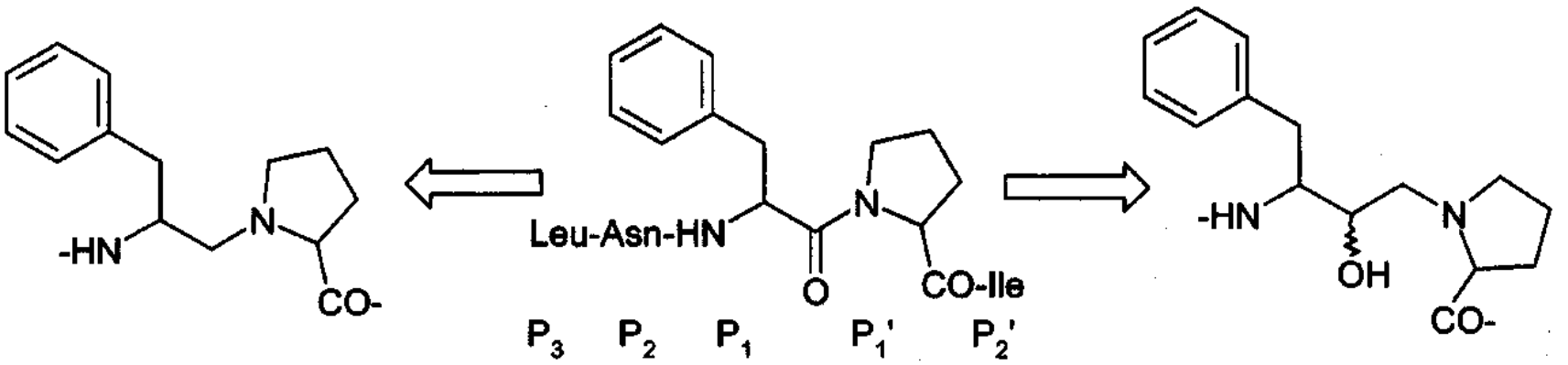
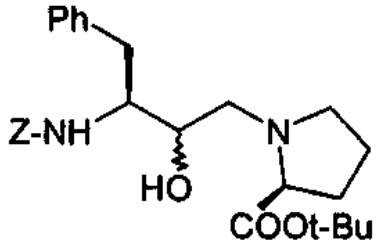
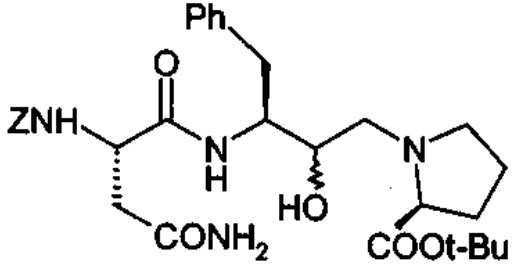
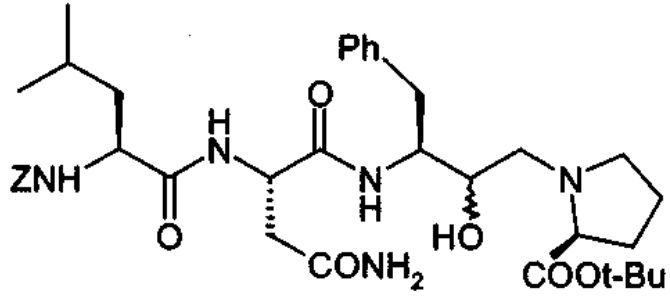


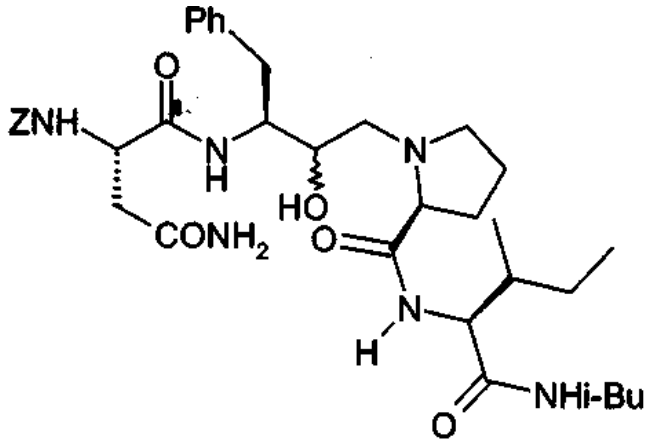
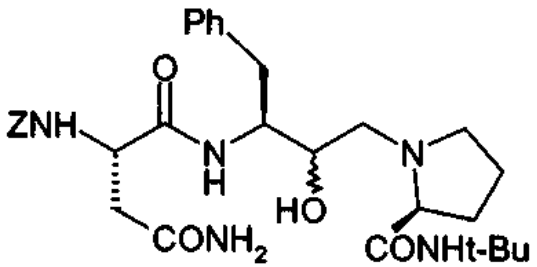
Figure 2 *Structures of HIV substrate and potential inhibitors*

HIV – Hemmstoff-Design

Table 1 *The identification of minimum inhibitor sequence*

Compound no	*Stereochemistry at -CHOH-*	*Structure*	*IC_{50} (nM) HIV-1*
1	*R*[a]		6500
2	*R*		140
3	*S*		300
4	*R*[a]		600

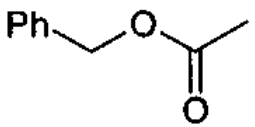
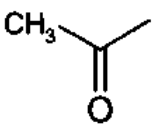
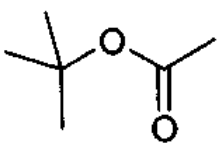
HIV – Hemmstoff-Design

5	R^a		130
6	R		210

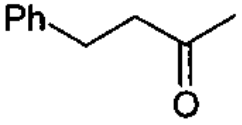
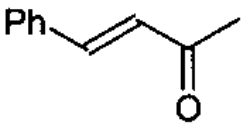
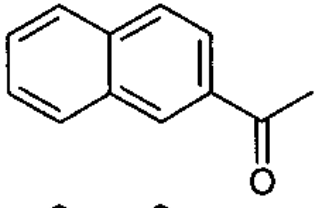
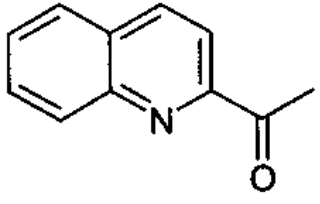
[a] More active diastereomer, probably *R*.

Optimierung des N-Terminus

Table 2 *The optimisation of N-terminus*

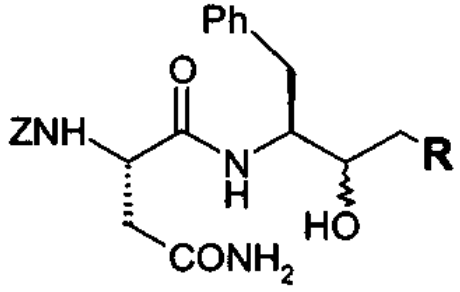
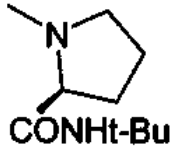
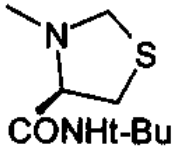
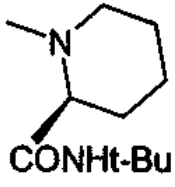
Compound no	*Structure R =*	*IC*$_{50}$ (nM *HIV-1*
2	 (Z)	140
7		8600
8	 (BOC)	8000

Optimierung des N-Terminus

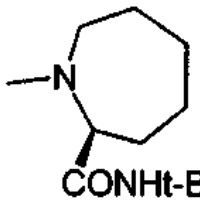
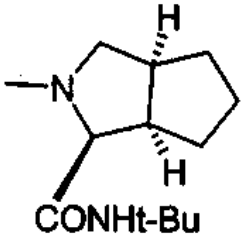
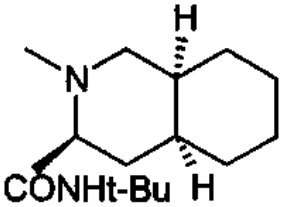
9		240
10		240
11		46
12		23

Prolin - Optimierung

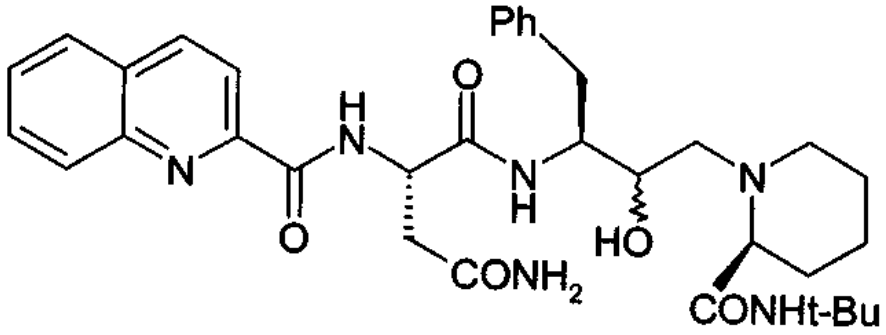
Table 3 *Proline optimisation*

Compound no	*Stereo-chemistry at -CHOH-*	*Structure R =*		IC_{50} (nM) *HIV-1*
6	*R*			210
13	*R*			8.4
14	*R*			18

Prolin - Optimierung

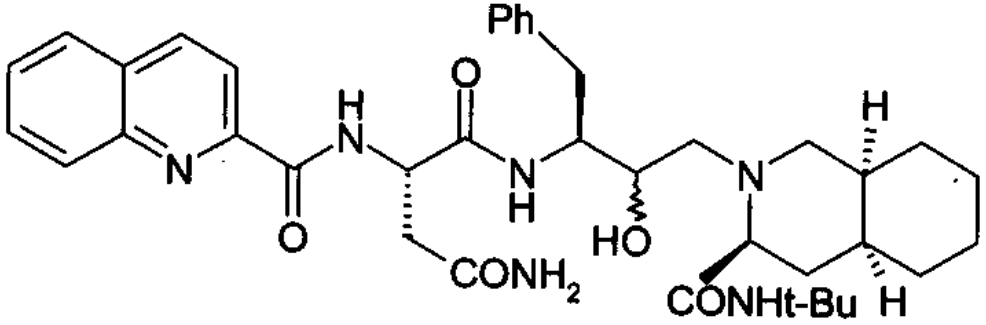
15	*R*		92
16	*R*		5.6
17	*R*		2.7
18	*S*		≫100

Resultat der Optimierung



19 R-isomer HIV-1 IC_{50} 2 nM

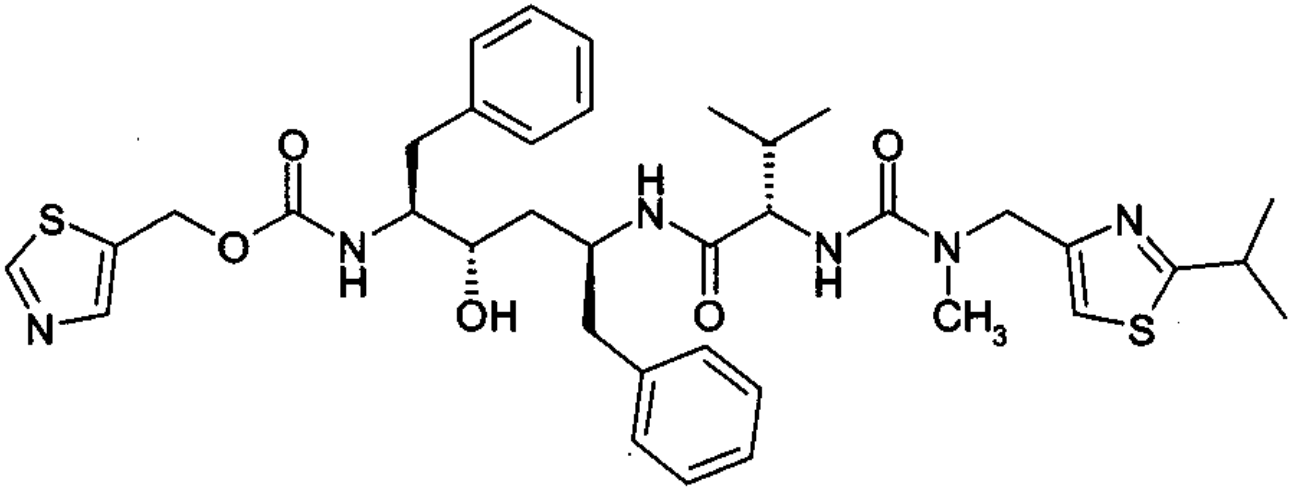
20 S-isomer HIV-1 IC_{50} 470 nM



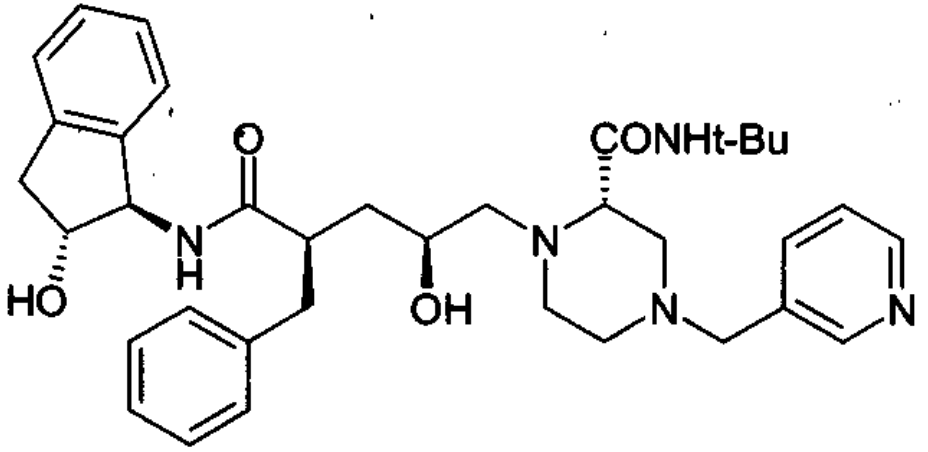
21 Ro 31-8959 (saquinavir) R-isomer HIV-1 IC_{50} <0.4 nM (Ki 0.12 nM)

22 S-isomer HIV-1 IC_{50} 620 nM

Weitere Präparate am Markt

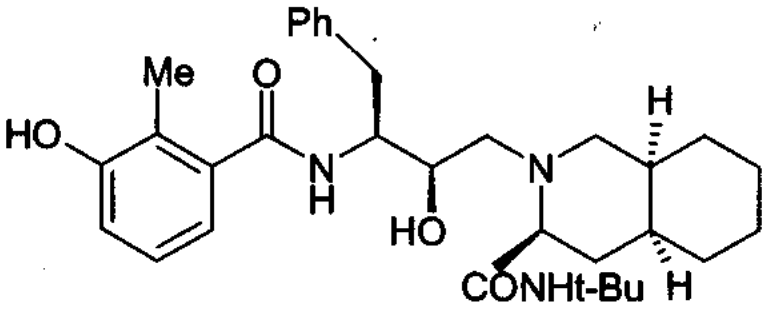


23 ritonavir

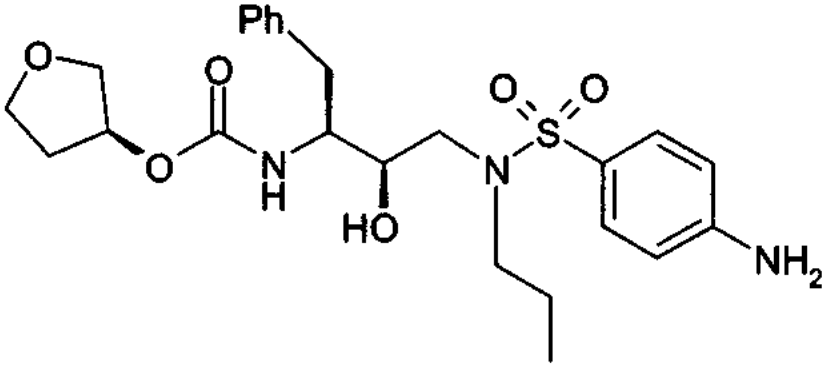


24 indinavir

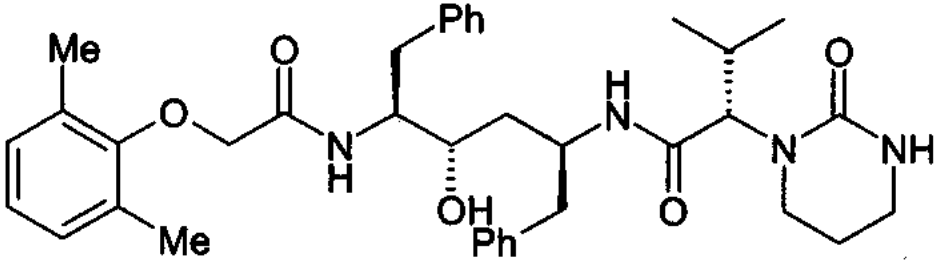
Weitere Präparate am Markt



25 nelfinavir



26 amprenavir



27 lopinavir

Röntgen - Struktur

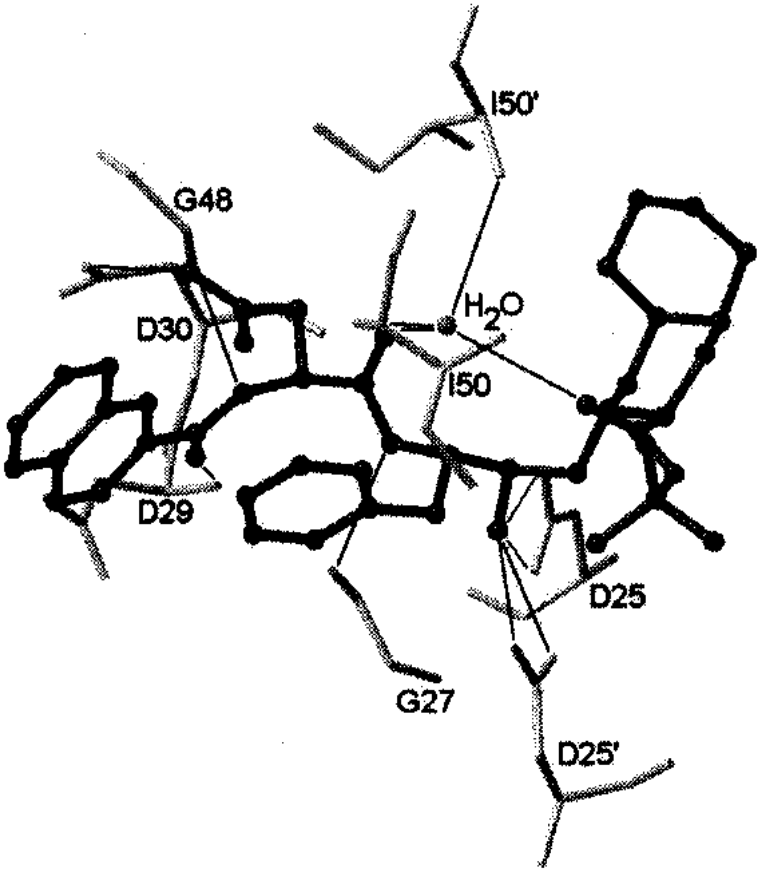


Figure 3 *X-ray structure of saquinavir* ***21*** *bound into the active site of HIV protease*

Röntgen - Struktur

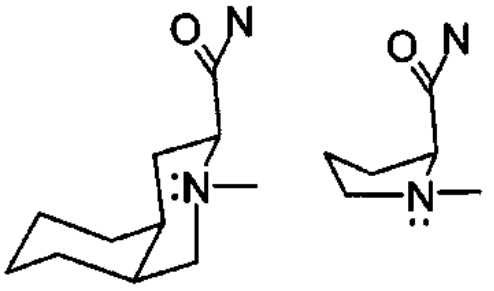
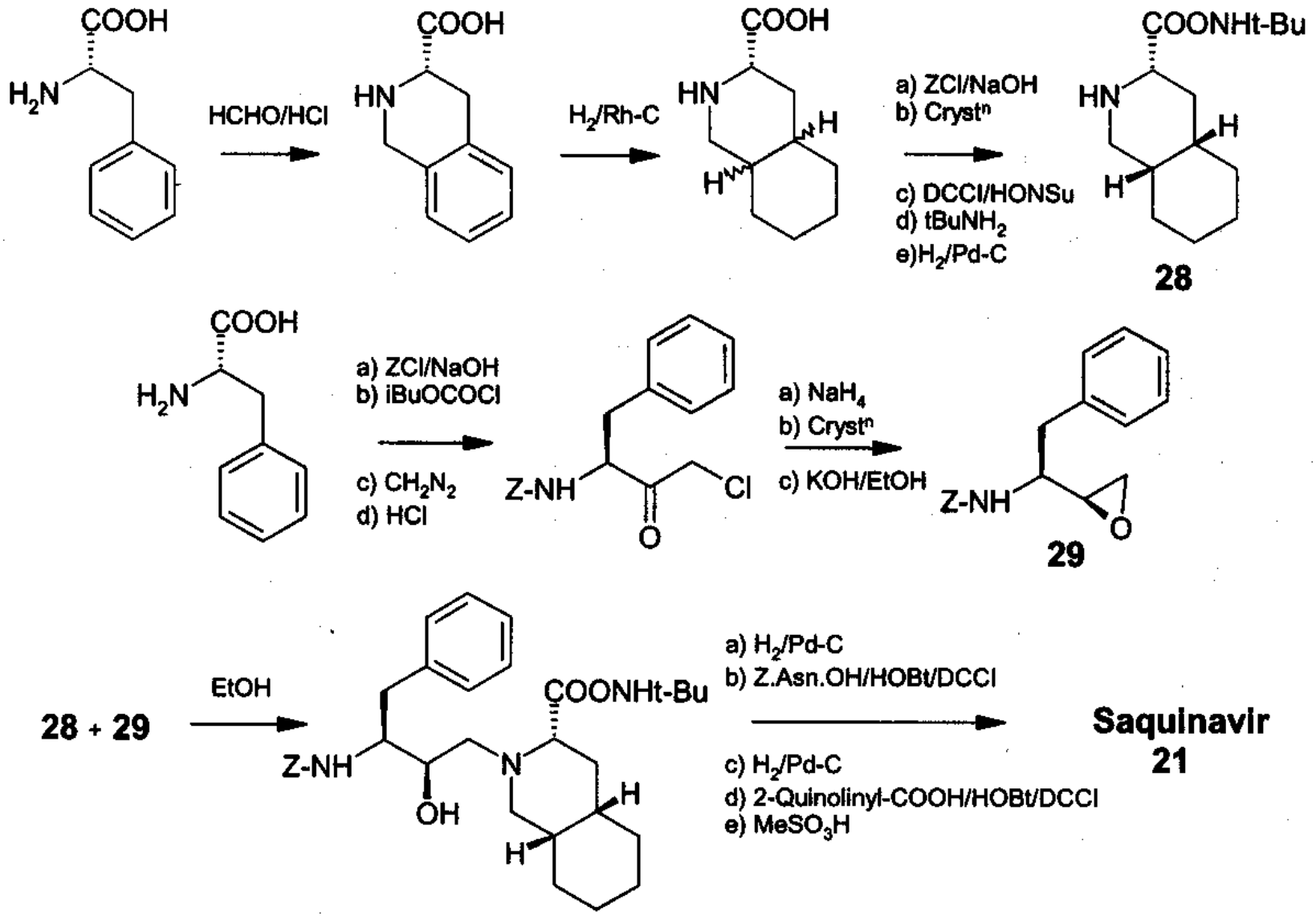


Figure 4 *Differing bound conformations of the proline and decahydroisoquinoline*

Saquinavir - Synthese



Saquinavir - Synthese

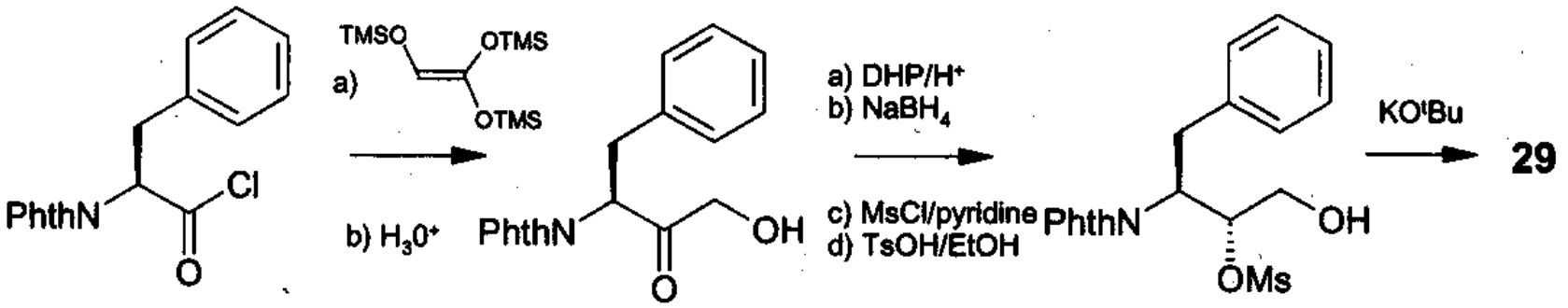
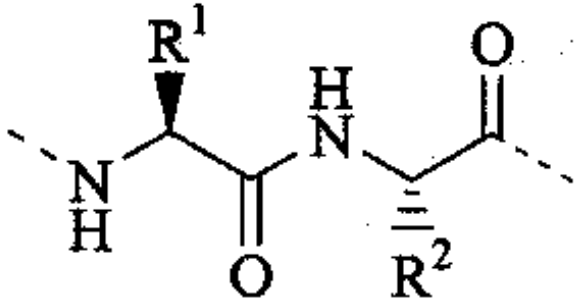
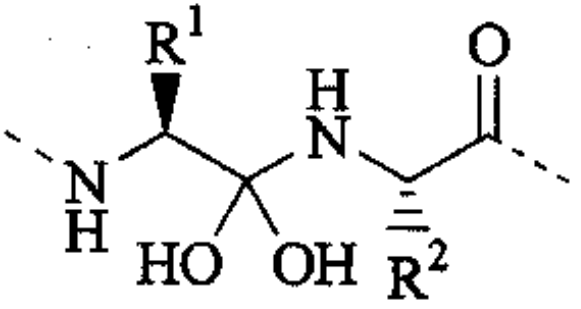


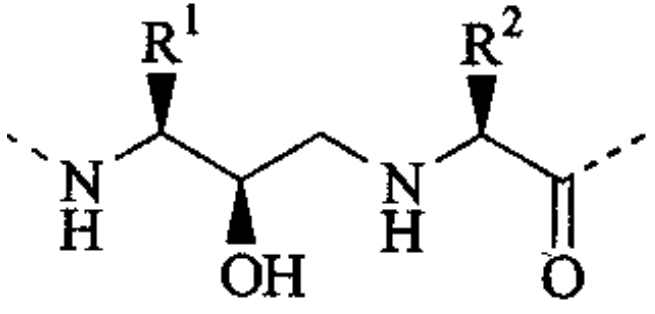
Figure 5 *Synthesis of saquinavir 21*



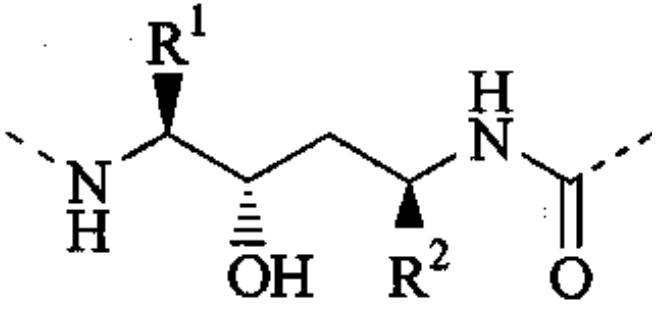
Cleavable dipeptide substrate



Amide cleavage transition state



Hydroxyethylamine dipeptide isostere



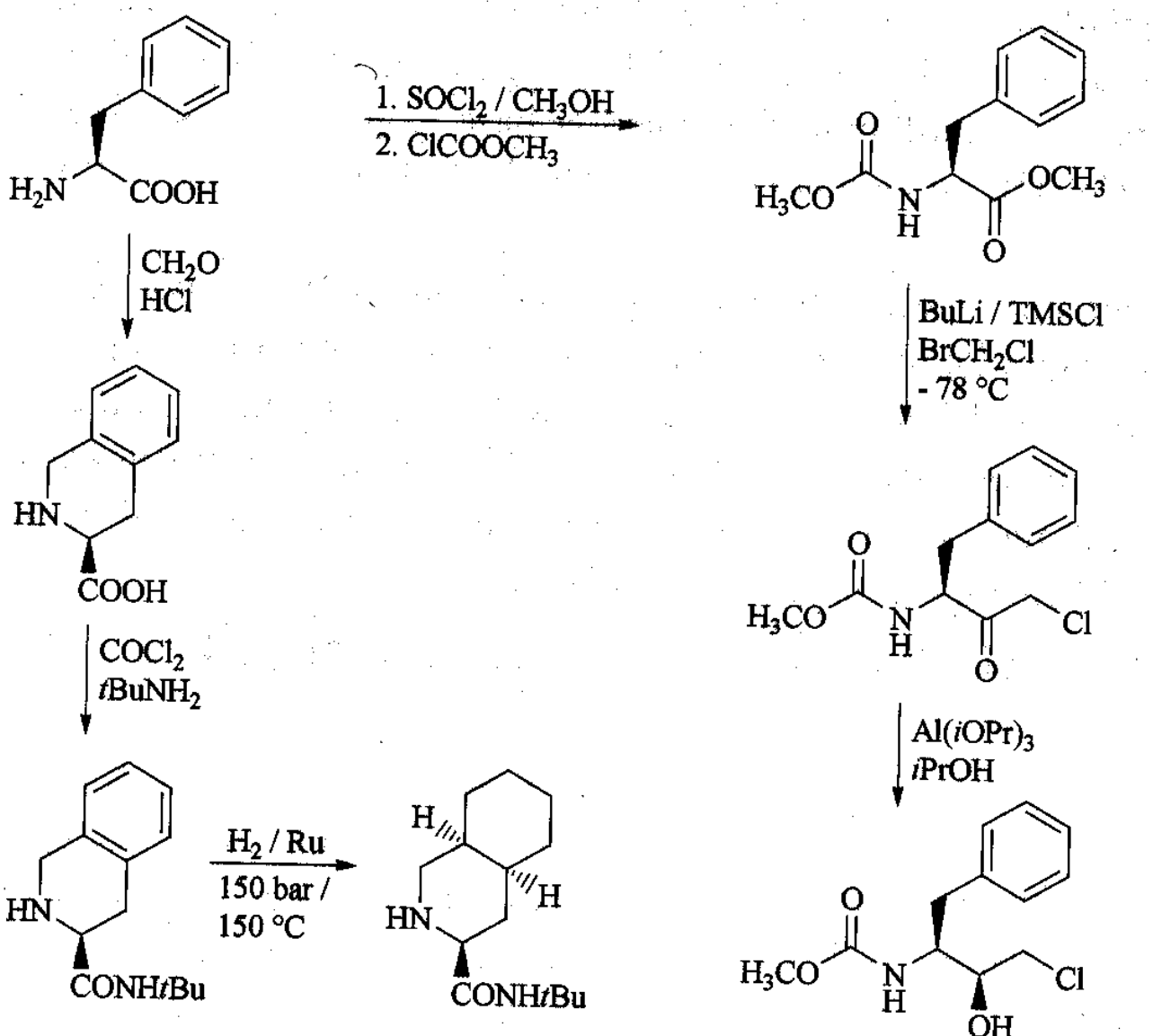
Hydroxyethylene dipeptide isostere

Molecular Conceptor:

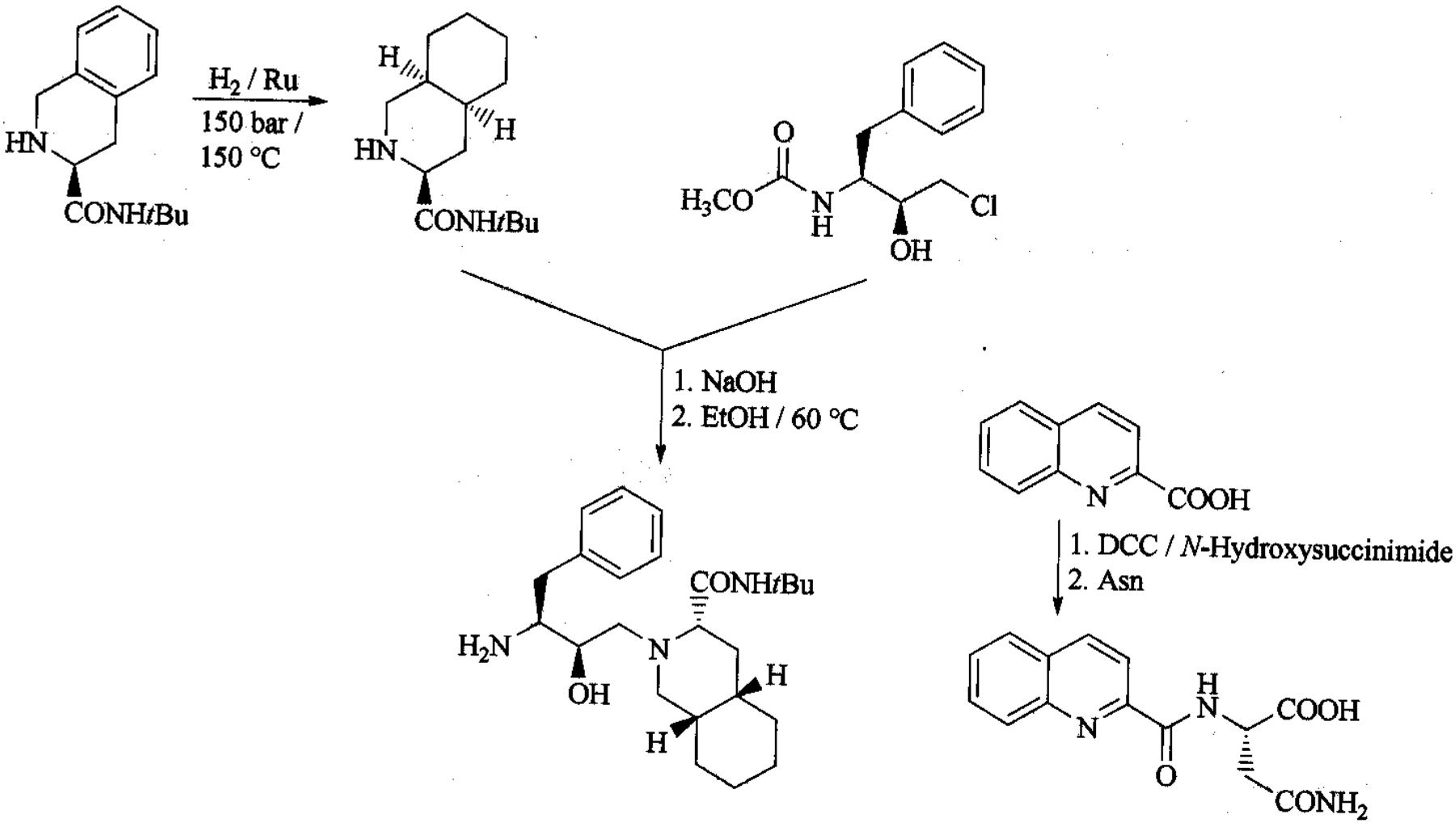
- Die Entwicklung von cyclischen Harnstoffen als Protease Hemmer

Protease-Hemmer

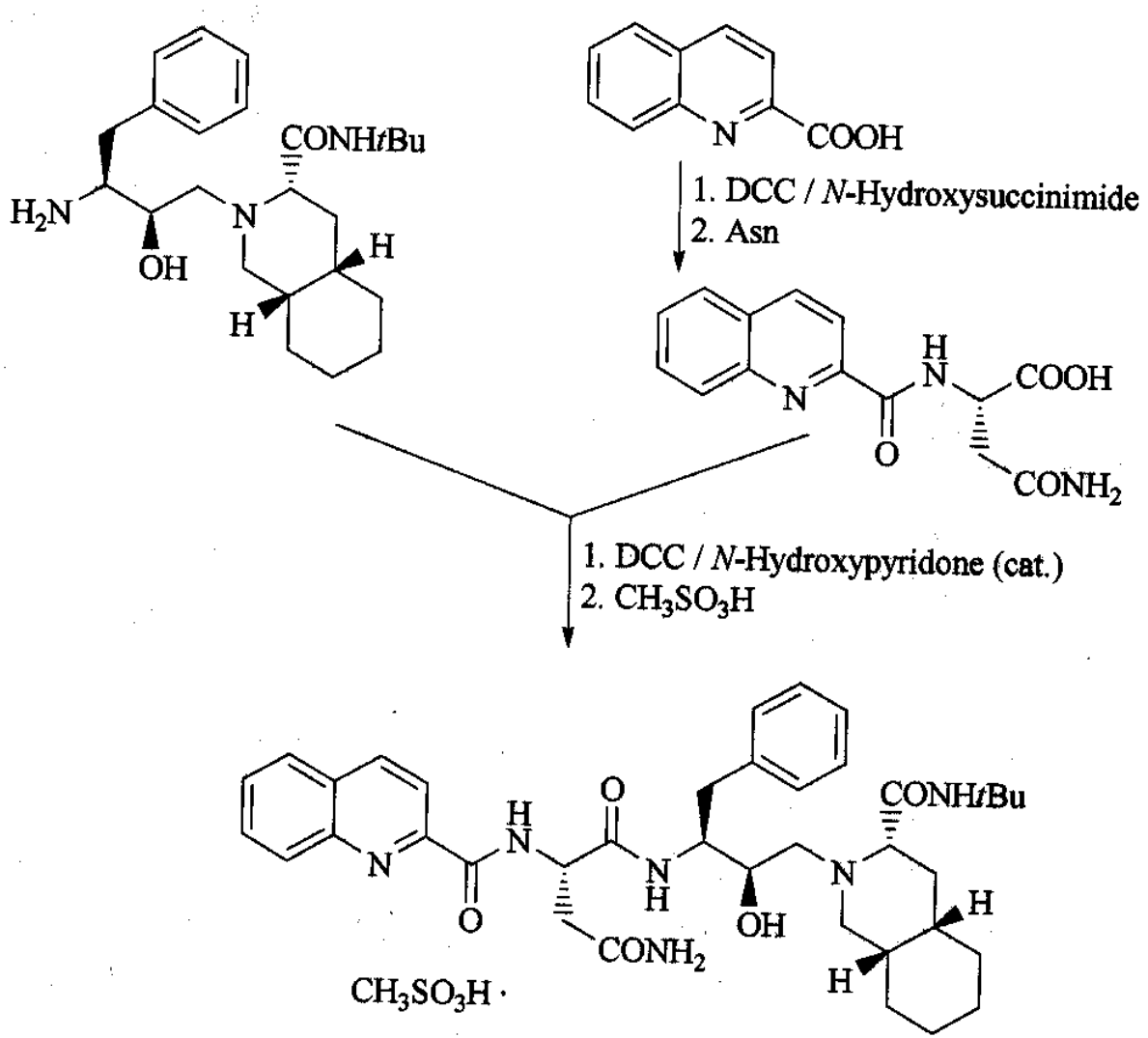
Saquinqvir


1. SOCl2 / CH3OH
2. ClCOOCH3
H2N
COOH
H3CO
N
H
OCH3
CH2O
HCl
BuLi / TMSCl
BrCH2Cl
- 78 °C
HN
COOH
Cl
COCl2
tBuNH2
Al(iOPr)3
iPrOH
H2 / Ru
150 bar /
150 °C
CONHtBu
OH

Saquinqvir

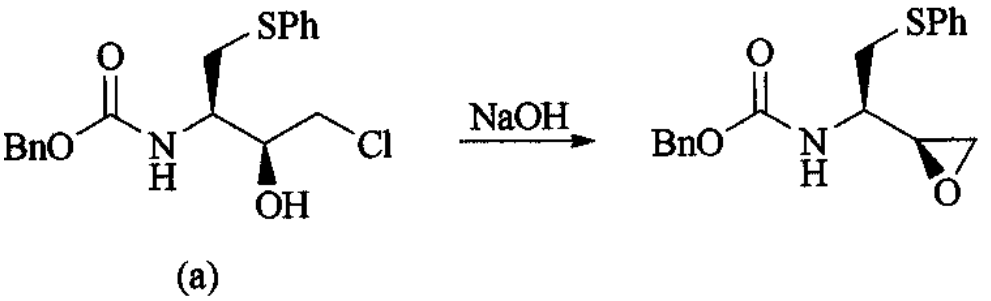

HN
CONHtBu
H2 / Ru
150 bar /
150 °C
H
H
HN
CONHtBu
H3CO
O
N
H
Cl
OH
1. NaOH
2. EtOH / 60 °C
H2N
OH
N
CONHtBu
H
H
N
COOH
1. DCC / N-Hydroxysuccinimide
2. Asn
N
H
N
COOH
O
CONH2

Saquinqvir

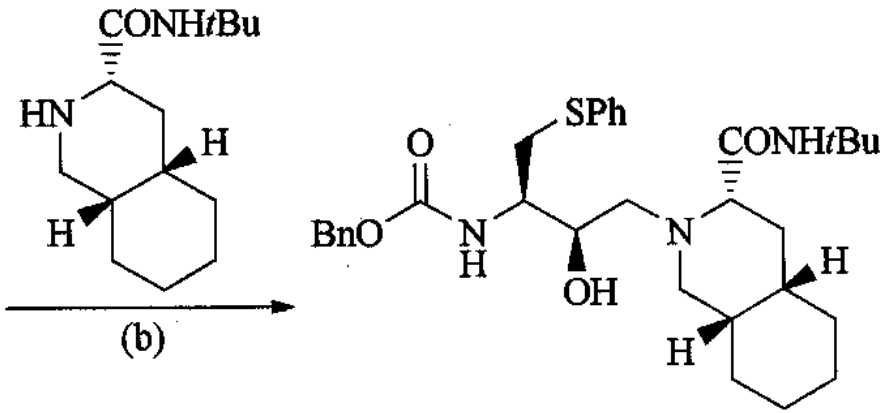


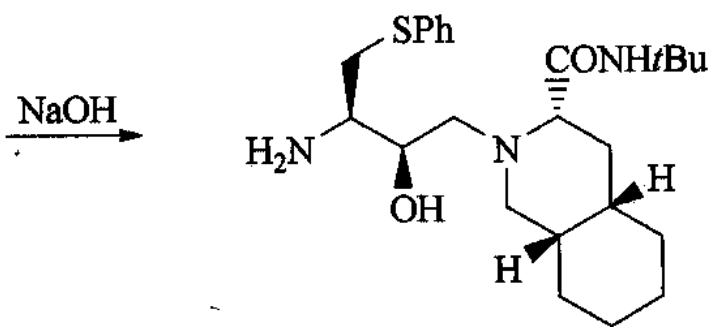
Saquinavir mesylate (Invirase)

Nelfinavir

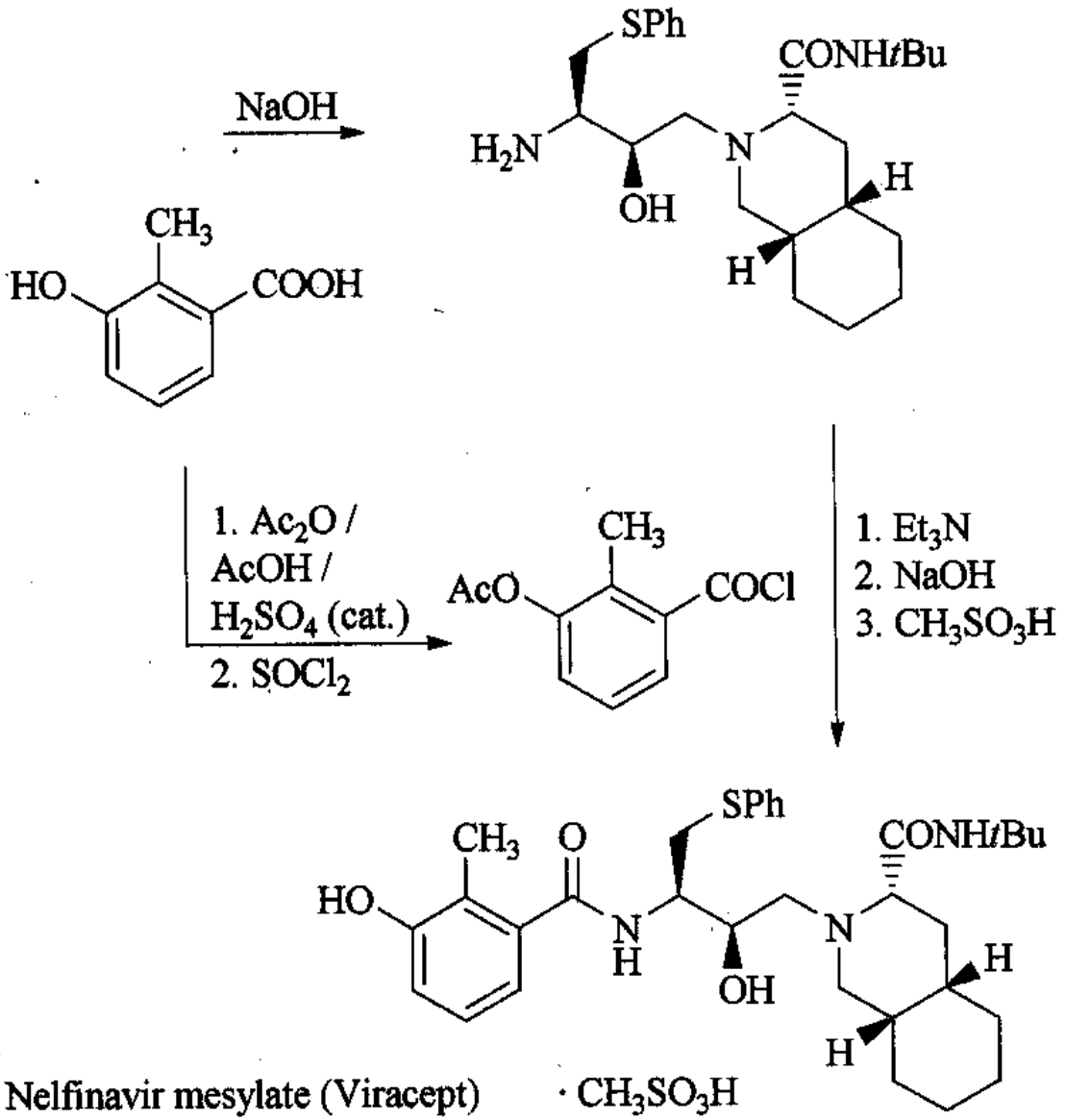


(a)



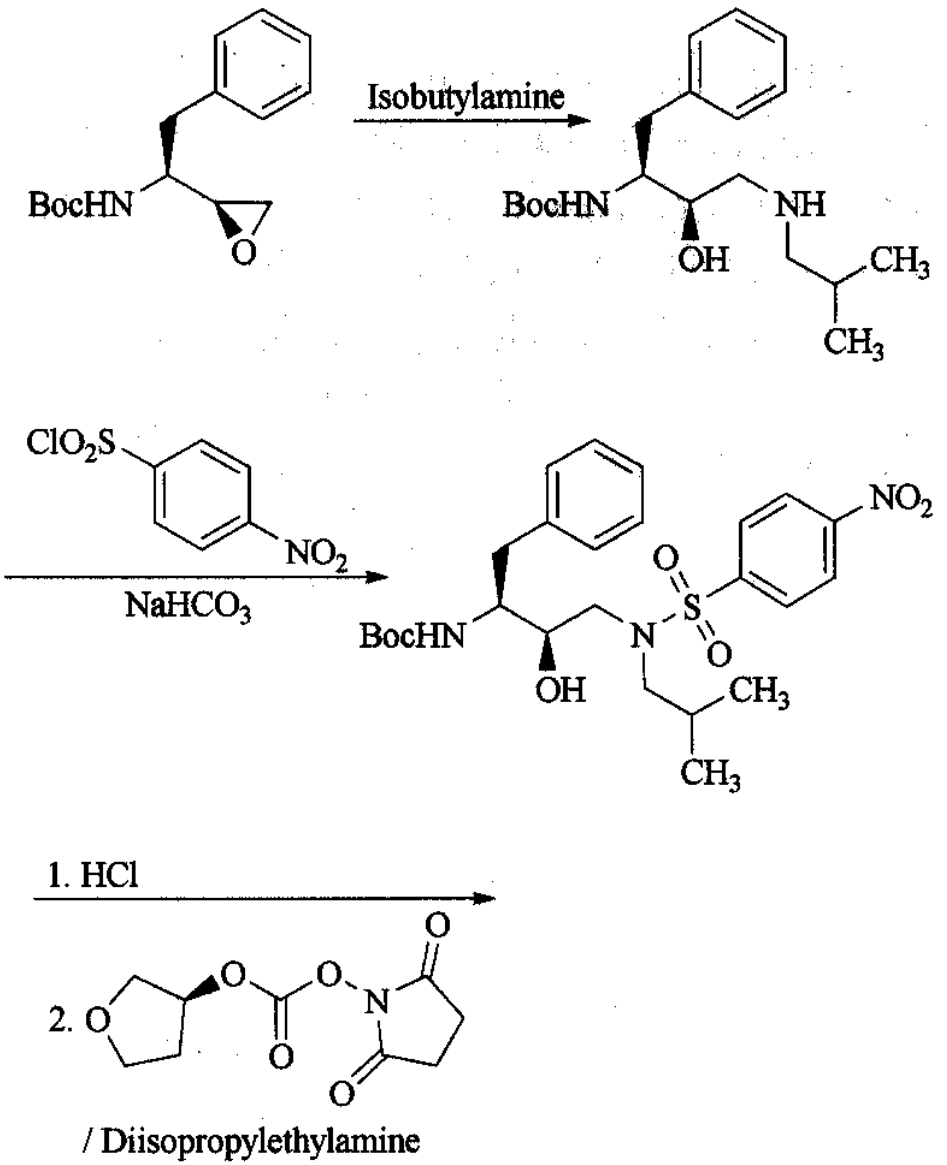


Nelfinavir

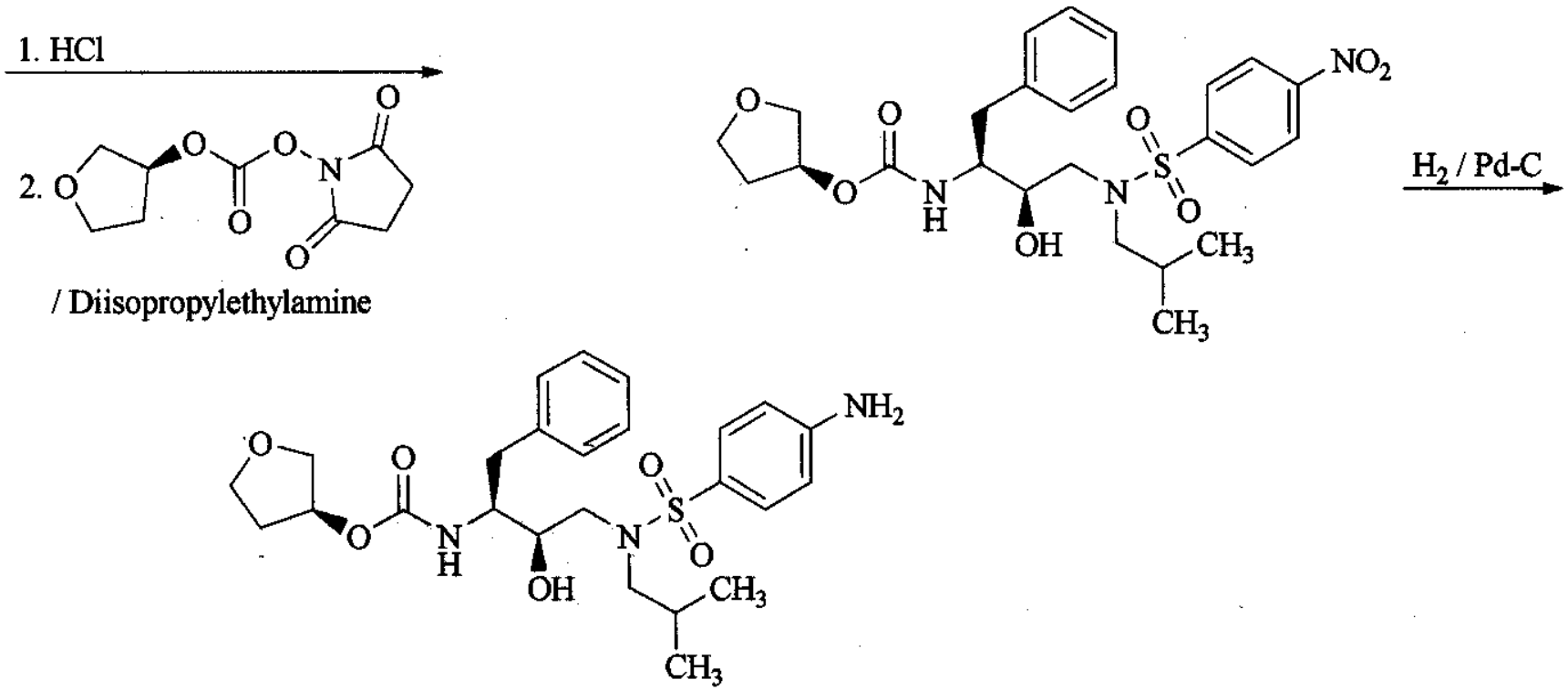


Nelfinavir mesylate (Viracept) · CH_3SO_3H

Amprenavir

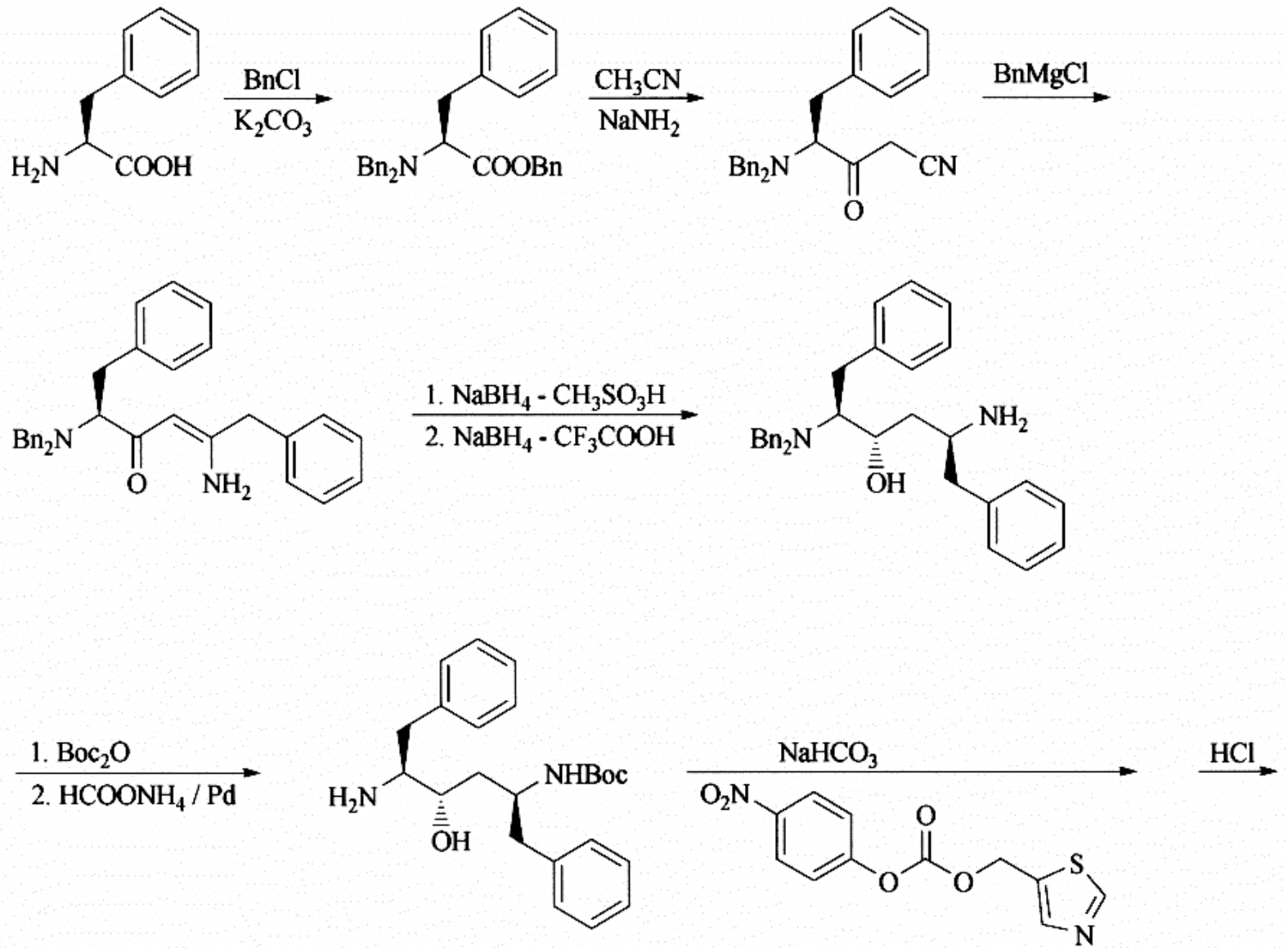

Isobutylamine
BocHN
O
BocHN
NH
OH
CH3
CH3
ClO2S
NO2
NaHCO3
NO2
BocHN
OH
O
S
O
N
CH3
CH3
1. HCl
2. O
O
O
O
N
O
O
/ Diisopropylethylamine

Amprenavir

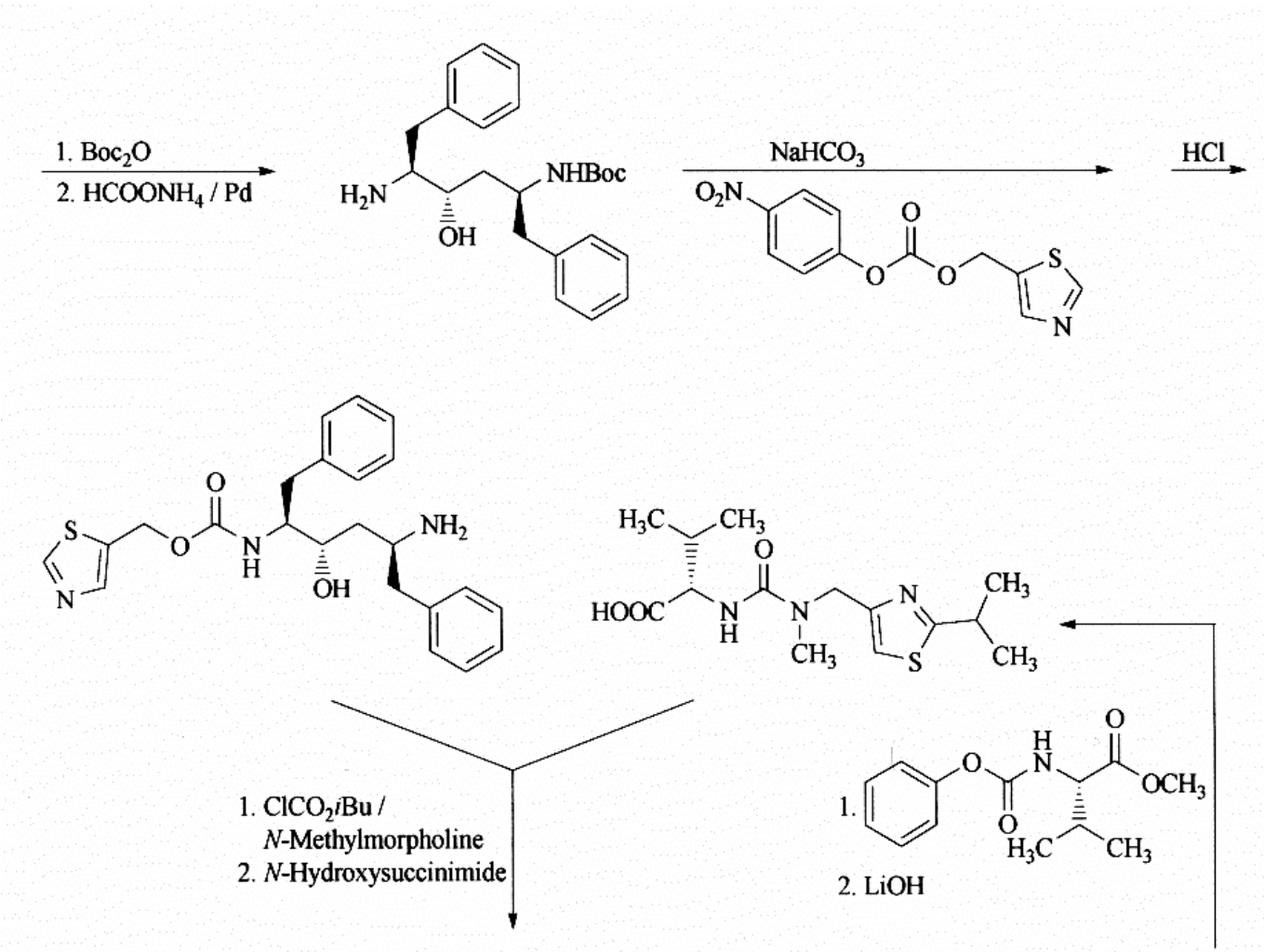


Trade name: Agenerase (Vertex Pharmaceuticals, USA; Glaxo Wellcome, UK; Kissei, Japan).

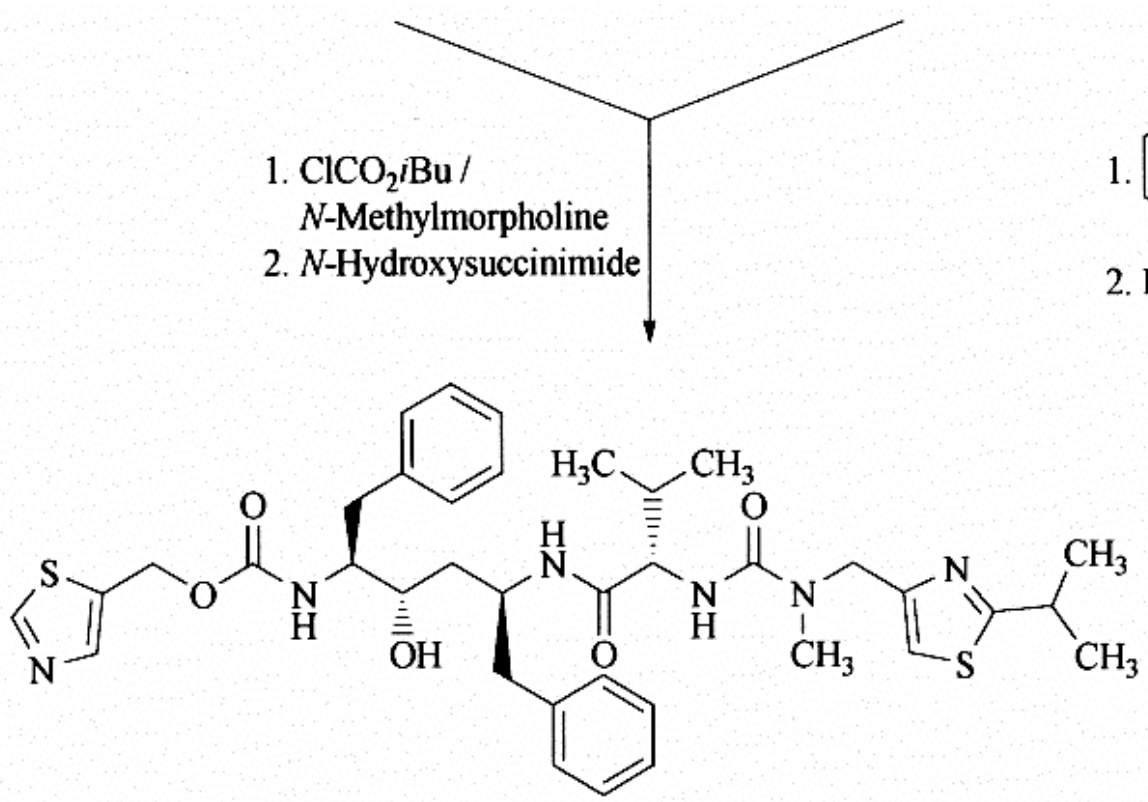
Ritonavir

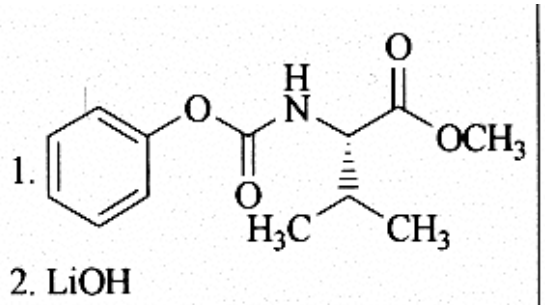

BnCl
K2CO3
CH3CN
NaNH2
BnMgCl
1. NaBH4 - CH3SO3H
2. NaBH4 - CF3COOH
1. Boc2O
2. HCOONH4 / Pd
NaHCO3
HCl

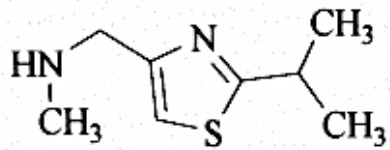
Ritonavir

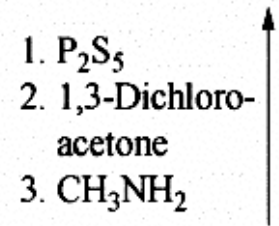

1. Boc2O
2. HCOONH4 / Pd
H2N
NHBoc
OH
NaHCO3
O2N
HCl
S
O
N
NH2
H3C
CH3
HOOC
CH3
1. ClCO2iBu /
N-Methylmorpholine
2. N-Hydroxysuccinimide
1.
OCH3
2. LiOH

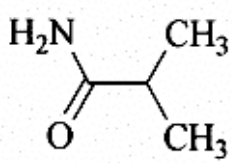
Ritonavir







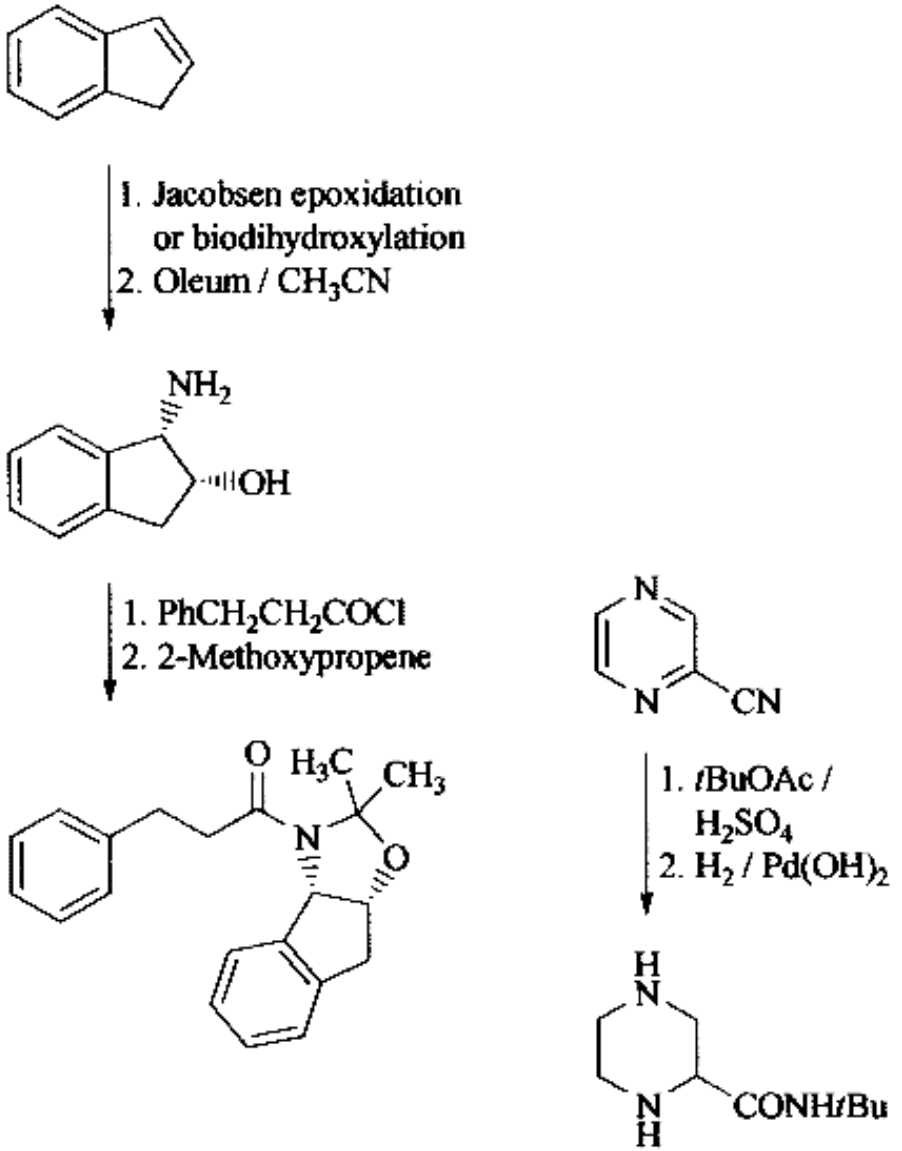




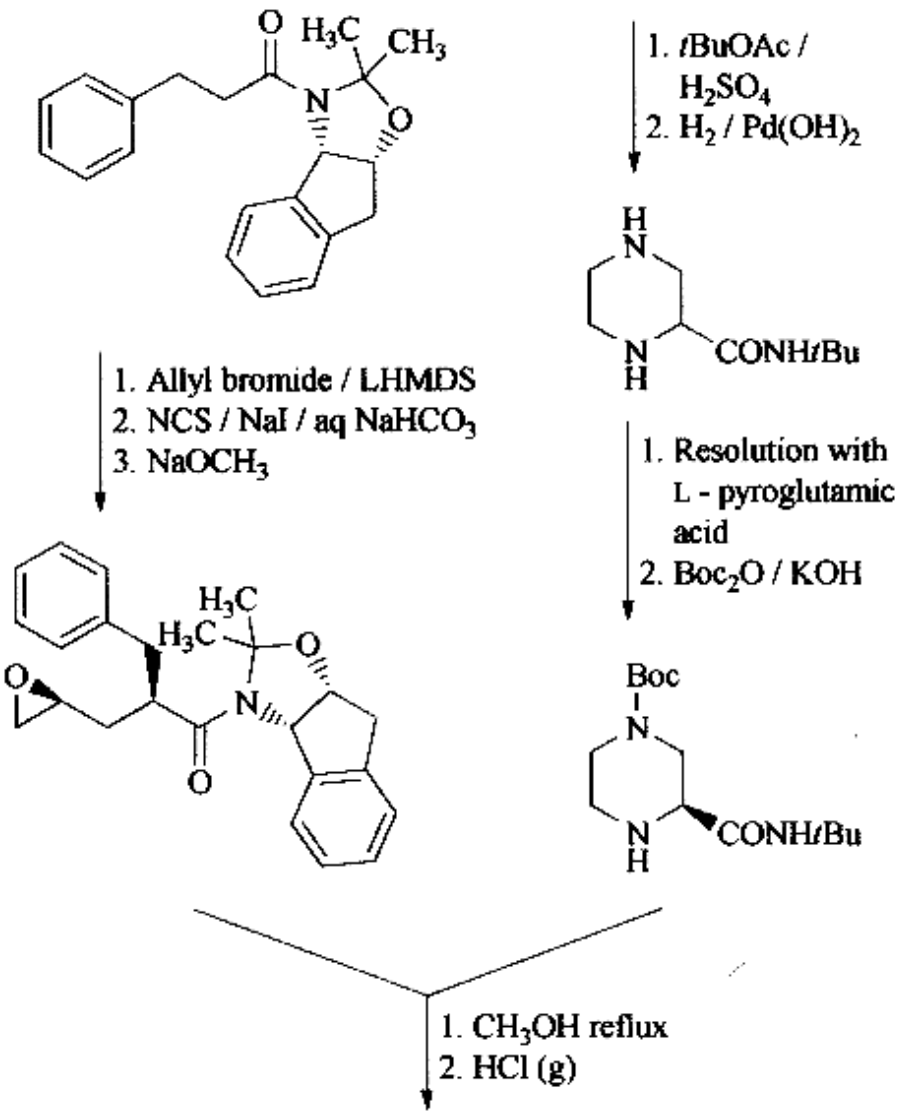
Ritonavir (Norvir)

Trade name: Norvir (Abbott, USA).

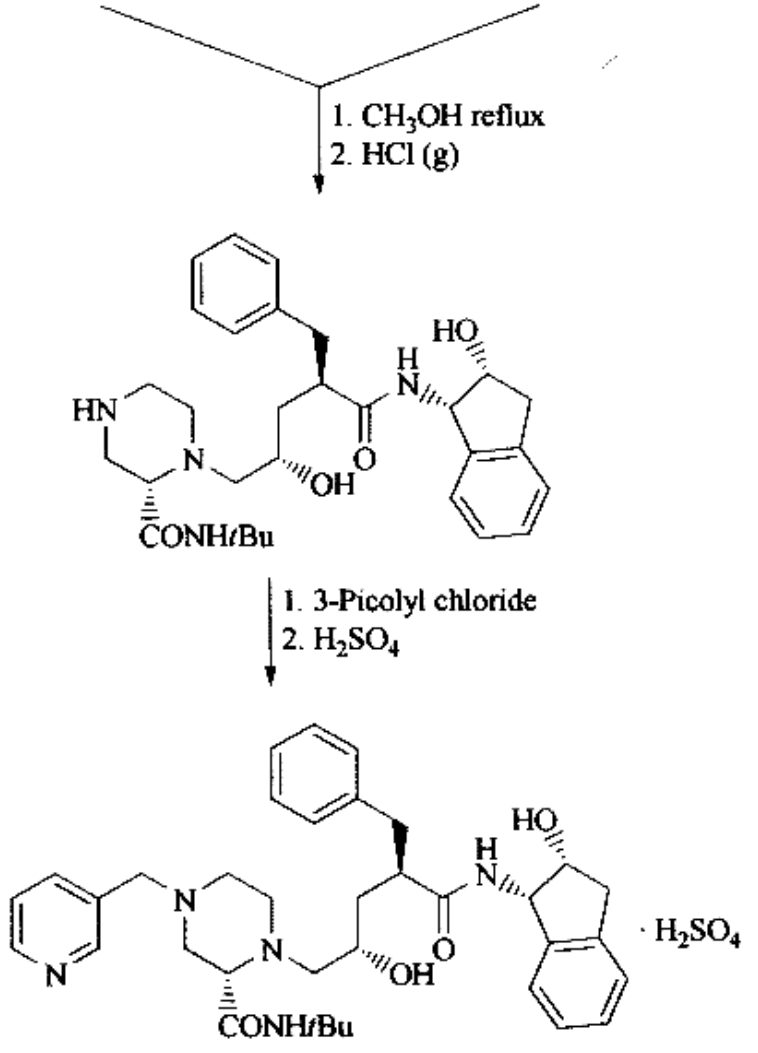
Crixivan


1. Jacobsen epoxidation
or biodihydroxylation
2. Oleum / CH_3CN
NH_2
OH
1. $PhCH_2CH_2COCl$
2. 2-Methoxypropene
O
H_3C
CH_3
N
O
N
N
CN
1. tBuOAc /
H_2SO_4
2. H_2 / $Pd(OH)_2$
H
N
N
H
CONHtBu

Crixivan


1. Allyl bromide / LHMDS
2. NCS / NaI / aq $NaHCO_3$
3. $NaOCH_3$
1. tBuOAc / H_2SO_4
2. H_2 / $Pd(OH)_2$
1. Resolution with L - pyroglutamic acid
2. Boc_2O / KOH
1. CH_3OH reflux
2. HCl (g)
CONHtBu
Boc

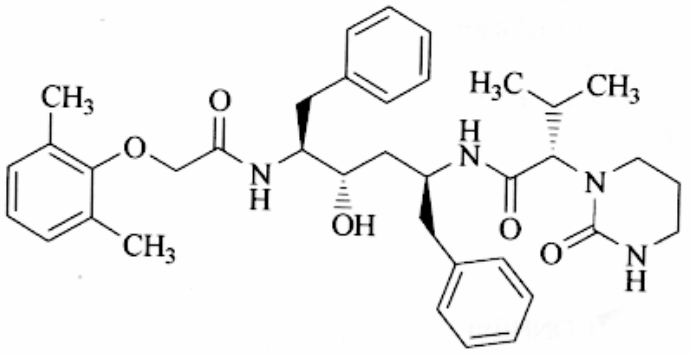
Crixivan



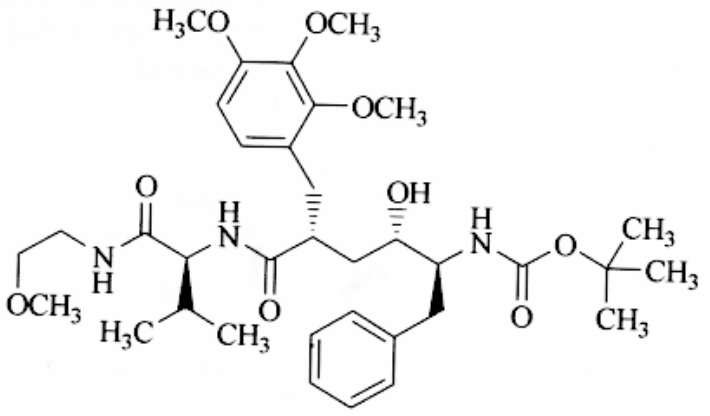
Indinavir sulfate (Crixivan)

Trade name (indinavir sulfate): Crixivan (Merck & Co. USA).

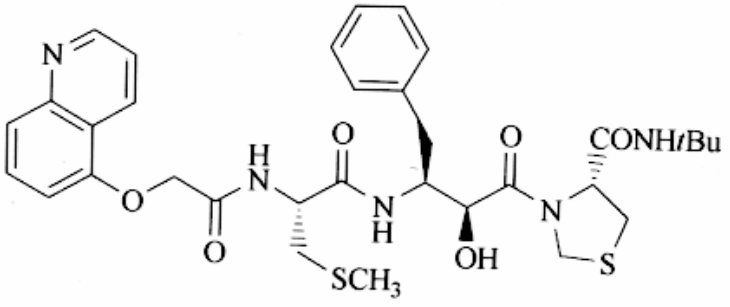
In klinischer Entwicklung



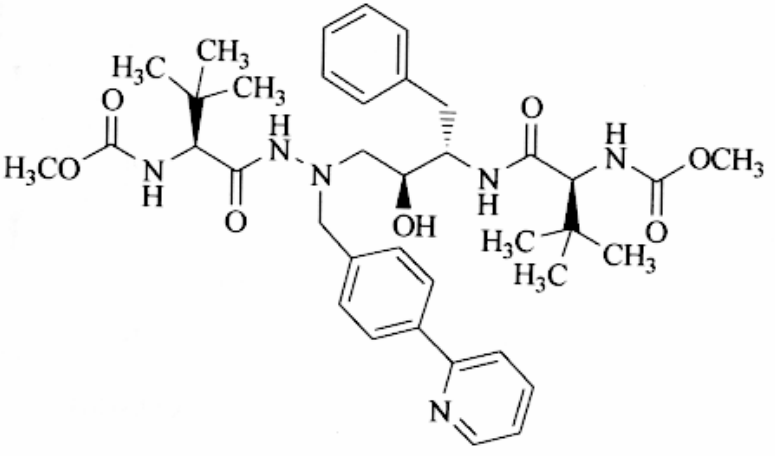
Lopinavir (ABT-378, Abbott, phase III)



Lasinavir (CGP-61755, BMS, phase I / II)

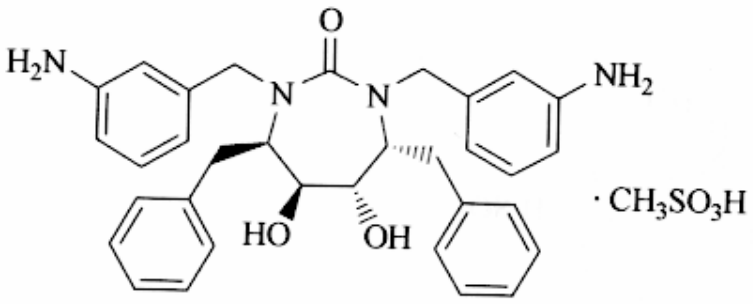


KNI-272 (Japan Energy Corporation, phase II)

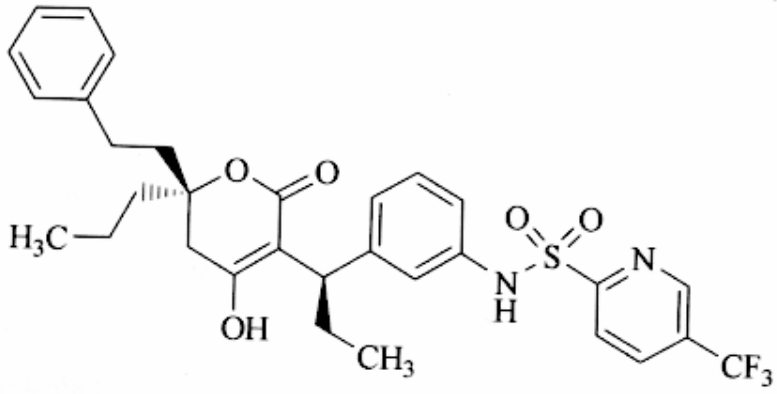


CGP-73547 (BMS, phase I)

In klinischer Entwicklung



DMP-450 (Triangle Pharmaceuticals, phase II)



Tipranavir (PNU 140690, Pharmacia & Upjohn, phase II)

Figure 3. HIV therapeutics in clinical development