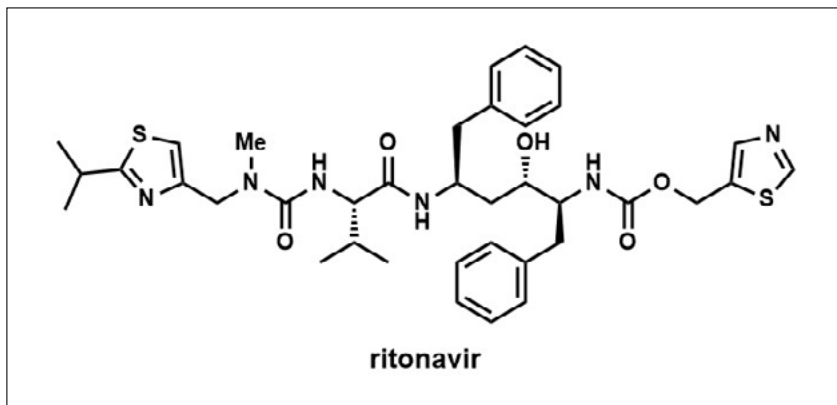


Ritonavir



SOS

Related reviews in Science of Synthesis

- Urea Derivatives
- Thiazoles
- Carbamic Acid Esters

Synonyms: A-84538, ABT-538

ATC: J05AE03

Use: AIDS therapeutic, antiviral, HIV-1-protease inhibitor

Chemical name: [5*S*-(5*R**,8*R**,10*R**,11*R**)]-10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oyl 5-thiazolylmethyl ester

Formula: C₃₇H₄₈N₆O₅S₂

MW: 720.96 g/mol

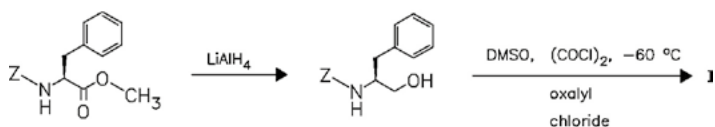
CAS-RN: 155213-67-5

InChI Key: NCDNXCXDXHOMX-XGKFQTDJSA-N

InChI: InChI=1S/C37H48N6O5S2/c1-24(2)33(42-36(46)43(5)20-29-22-49-35(40-29)25(3)4)34(45)39-28(16-26-12-8-6-9-13-26)18-32(44)31(17-27-14-10-7-11-15-27)41-37(47)48-21-30-19-38-23-50-30/h6-15,19,22-25,28,31-33,44H,16-18,20-21H2,1-5H3,(H,39,45)(H,41,47)(H,42,46)/t28-,31-,32-,33-/m0/s1

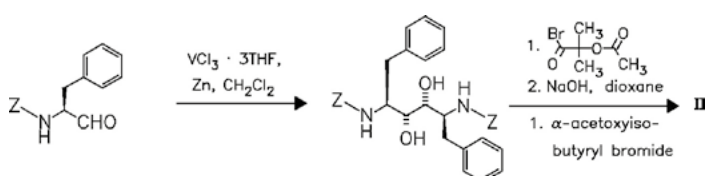
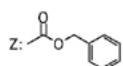
Synthesis Path

a



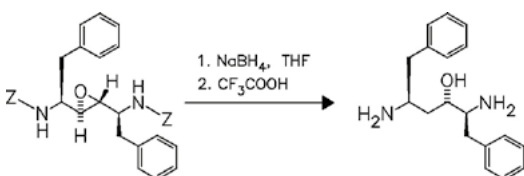
N-(benzyloxycarbonyl)-L-phenylalanine methyl ester

N-(benzyloxycarbonyl)-L-phenylalaninol



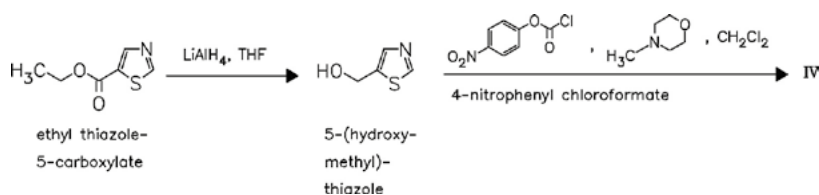
N-(benzyloxycarbonyl)-L-phenylalaninol (I)

(2S,3R,4R,5S)-2,5-bis[(benzyloxycarbonyl)amino]-3,4-dihydroxy-1,6-diphenylhexane



(2S,3R,4R,5S)-2,5-bis[(benzyloxycarbonyl)amino]-3,4-epoxy-1,6-diphenylhexane (II)

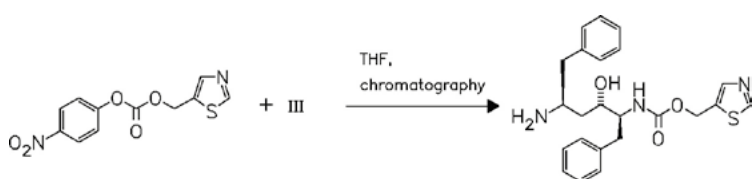
(2S,3S,5S)-2,5-diamino-3-hydroxy-1,6-diphenylhexane (III)



ethyl thiazole-5-carboxylate

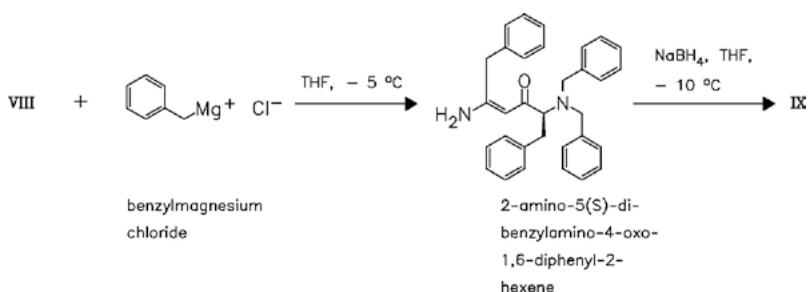
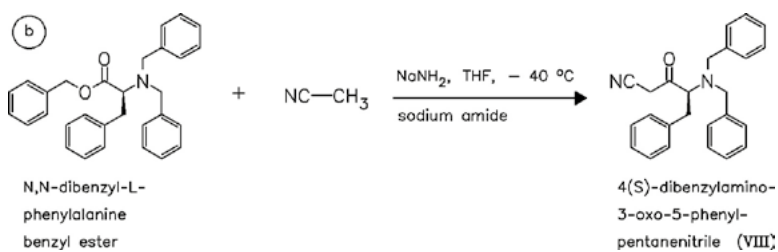
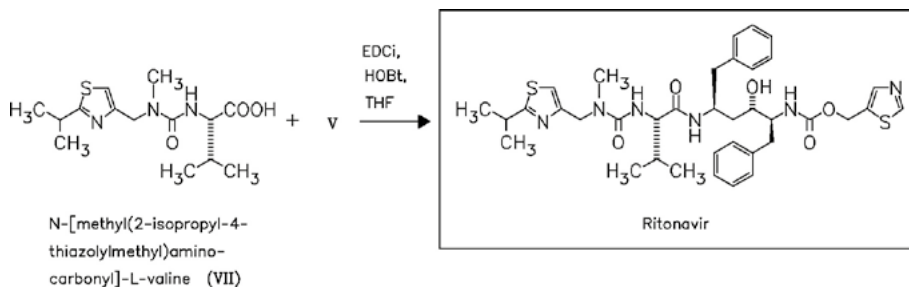
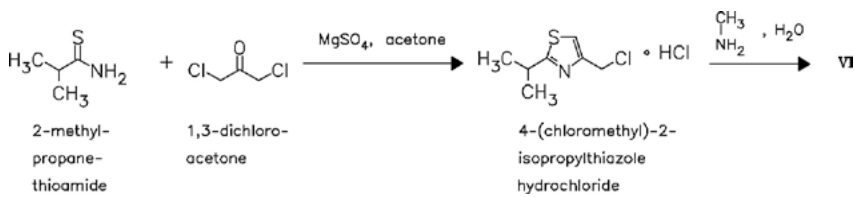
5-(hydroxymethyl)-thiazole

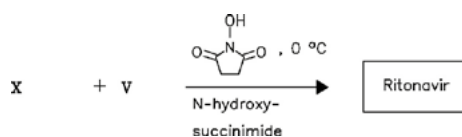
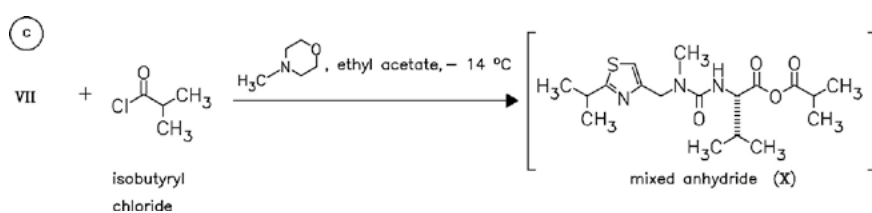
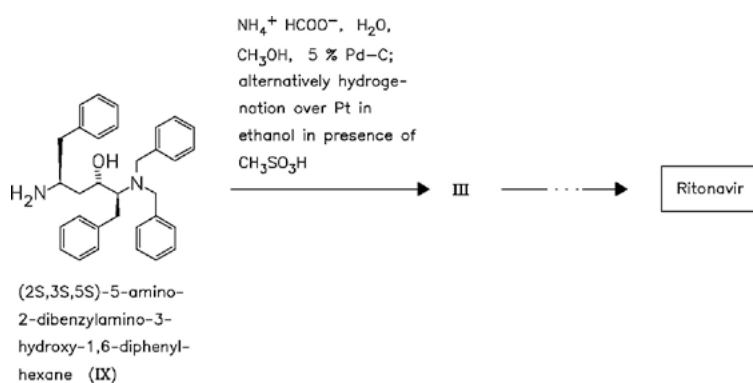
4-nitrophenyl chloroformate



5-thiazolylmethyl 4-nitrophenyl carbonate (IV)

(2S,3S,5S)-5-amino-2-(5-thiazolylmethoxycarbonyl-amino)-3-hydroxy-1,6-diphenylhexane (V)





Substances Referenced in Synthesis Path

CAS-RN	Formula	Chemical Name	CAS Index Name
75-05-8	C ₂ H ₃ N	acetonitrile	Acetonitrile
156732-15-9	C ₃₂ H ₃₆ N ₂ O	(2S,3S,5S)-5-amino-2-dibenzylamino-3-hydroxy-1,6-diphenylhexane	Benzenebutanol, γ-amino-α-[1-bis(phenylmethyl)amino]-2-phenylethyl]-, [αS-[αR*(R*),γR*]]-
156732-13-7	C ₃₂ H ₃₂ N ₂ O	2-amino-5(S)-dibenzylamino-4-oxo-1,6-diphenyl-2-hexene	4-Hexen-3-one, 5-amino-2-[bis(phenylmethyl)amino]-1,6-diphenyl-, (S)-
144164-11-4	C ₂₃ H ₂₇ N ₃ O ₃ S	(2S,3S,5S)-5-amino-2-(5-thiazolylmethoxycarbonylamino)-3-hydroxy-1,6-diphenylhexane	Carbamic acid, [4-amino-2-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]-, 5-thiazolylmethyl ester, [1S-(1R*,2R*,4R*)]-
6921-34-2	C ₇ H ₇ ClMg	benzylmagnesium chloride	Magnesium, chloro(phenylmethyl)-
59830-60-3	C ₁₇ H ₁₇ NO ₃	N-(benzyloxycarbonyl)-L-phenylalaninal	
35909-92-3	C ₁₈ H ₁₉ NO ₄	N-(benzyloxycarbonyl)-L-phenylalanine methyl ester	
6372-14-1	C ₁₇ H ₁₉ NO ₃	N-(benzyloxycarbonyl)-L-phenylalaninol	
137649-69-5	C ₃₄ H ₃₆ N ₂ O ₆	(2S,3R,4R,5S)-2,5-bis[(benzyloxycarbonyl)amino]-3,4-dihydroxy-1,6-diphenylhexane	
162849-92-5	C ₃₄ H ₃₄ N ₂ O ₅	(2S,3R,4R,5S)-2,5-bis[(benzyloxycarbonyl)amino]-3,4-epoxy-1,6-diphenylhexane	
65386-28-9	C ₇ H ₁₁ Cl ₂ NS	4-(chloromethyl)-2-isopropylthiazole hydrochloride	Thiazole, 4-(chloromethyl)-2-(1-methylethyl)-, hydrochloride
144163-44-0	C ₁₈ H ₂₄ N ₂ O	(2S,3S,5S)-2,5-diamino-3-hydroxy-1,6-diphenylhexane	Benzenebutanol, γ-amino-α-(1-amino-2-phenylethyl)-, [αS-[αR*(R*),γR*]]-
156732-12-6	C ₂₅ H ₂₄ N ₂ O	4(S)-dibenzylamino-3-oxo-5-phenylpentanenitrile	Benzenebutanenitrile, γ-[bis(phenylmethyl)amino]-β-oxo-, (S)-
111138-83-1	C ₃₀ H ₂₉ NO ₂	N,N-dibenzyl-L-phenylalanine benzyl ester	L-Phenylalanine, N,N-bis(phenylmethyl)-, phenylmethyl ester
534-07-6	C ₃ H ₄ Cl ₂ O	1,3-dichloroacetone	2-Propanone, 1,3-dichloro-
32955-22-9	C ₆ H ₇ NO ₂ S	ethyl thiazole-5-carboxylate	5-Thiazolecarboxylic acid, ethyl ester
38585-74-9	C ₄ H ₅ NOS	5-(hydroxymethyl)thiazole	5-Thiazolemethanol
6066-82-6	C ₄ H ₅ NO ₃	N-hydroxysuccinimide	2,5-Pyrrolidinedione, 1-hydroxy-
79-30-1	C ₄ H ₇ ClO	isobutyryl chloride	Propanoyl chloride, 2-methyl-
154212-60-9	C ₈ H ₁₄ N ₂ S	2-isopropyl-4-(methylaminomethyl)thiazole	4-Thiazolemethanamine, N-methyl-2-(1-methylethyl)-
74-89-5	CH ₅ N	methylamine	Methanamine
154212-61-0	C ₁₄ H ₂₃ N ₃ O ₃ S	N-[methyl(2-isopropyl-4-thiazolylmethyl)aminocarbonyl]-L-valine	L-Valine, N-[[methyl[[2-(1-methylethyl)-4-thiazolyl]methyl]amino]carbonyl]-
13515-65-6	C ₄ H ₉ NS	2-methylpropanethioamide	Propanethioamide, 2-methyl-
162537-10-2	C ₁₃ H ₁₆ N ₂ O ₆	N-[(4-nitrophenoxy)carbonyl]-L-valine methyl ester	L-Valine, N-[(4-nitrophenoxy)carbonyl]-, methyl ester
7693-46-1	C ₇ H ₄ ClNO ₄	4-nitrophenyl chloroformate	Carbonochloridic acid, 4-nitrophenyl ester
79-37-8	C ₂ Cl ₂ O ₂	oxalyl chloride	Ethanedioyl dichloride
144163-97-3	C ₁₁ H ₈ N ₂ O ₅ S	5-thiazolylmethyl 4-nitrophenyl carbonate	Carbonic acid, 4-nitrophenyl 5-thiazolylmethyl ester

Trade Names

Country	Trade Name	Vendor	Annotation
D	Kaletra	Abbott	comb.
	Norvir	Abbott	
F	Kaletra	Abbott	
	Norvir	Boehringer Ingelheim	
GB	Norvir	Abbott	
I	Kaletra	Abbott	comb.
	Norvir	Abbott	
J	Norvir	Dainabott-Dainippon	
USA	Kaletra	Abbott	comb.
	Norvir	Abbott	

Formulations

cps. 100 mg wfm; sol. 600 mg/7.5 ml, 8%

References

Kempf, D.J. et al.: J. Med. Chem. (JMCMAR) **41**, 602 (1998).

a, b US 5 635 523 (Abbott; 3.6.1997; appl. 6.4.1995; USA-prior. 23.5.1989, 8.9.1989, 22.12.1989, 9.5.1990, 20.11.1990, 15.8.1991, 23.10.1991, 29.12.1992, 2.12.1993).

WO 9 414 436 (Abbott Labs.; appl. 16.12.1993; USA-prior. 29.12.1992, 2.12.1993).

b WO 9 511 224 (Abbott Labs.; appl. 26.9.1994; USA-prior. 22.10.1993, 27.7.1994).

WO 9 604 232 (Abbott Labs.; appl. 17.7.1995; USA-prior. 29.7.1994).

c US 5 567 823 (Abbott Labs; 22.10.1996; appl. 6.6.1995; USA-prior. 6.6.1995).

polymorphs:

Chemburkar, S.R. et al.: Org. Process Res. Dev. (OPRDFK) **4**, 43 (2000).

pharmaceutical composition in alcoholic/organic solvent:

WO 9 507 696 (Abbott Labs.; appl. 30.4.1994; USA-prior. 13.9.1993, 28.1.1994, 15.8.1994).

WO 9 520 384 (Abbott Labs.; appl. 3.1.1995; USA-prior. 29.7.1994, 28.1.1994, 12.5.1995).

use for treating HIV:

WO 9 701 349 (Abbott Labs.; appl. 28.6.1996; USA-prior. 15.9.1995, 29.6.1995).

combination with lamivudine:

WO 9 626 734 (Glaxo; appl. 22.2.1996; GB-prior. 25.2.1995).

combination of HIV protease inhibitors:

WO 9 604 913 (Merck & Co.; appl. 7.8.1995; USA-prior. 20.7.1995, 11.8.1994, 14.11.1994).

EP 691 345 (Bristol-Myers Squibb; appl. 5.7.1995; USA-prior. 17.5.1995, 5.7.1994, 31.7.1987).

pharmaceutical composition with improved oral bioavailability:

WO 9 509 614 (Abbott Labs.; appl. 9.9.1994; USA-prior. 31.8.1994).